GLYCEMIC INDEX IN THE MANAGEMENT OF OBESITY AND METABOLIC SYNDROME.

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Glycemic index in the management of Obesity and Metabolic syndrome

THESIS

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Que aquest treball, titulat **"Glycemic index in the management of Obesity and Metabolic syndrome"**, que presenta el Sr. Martí Juanola Falgarona per obtenir el títol de Doctor, ha estat realitzat sota la meva direcció en el Departament de Bioquímica i Biotecnologia d'aquesta Universitat i que acompleix els requeriments per poder optar a Menció Internacional.

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ABBREBIATIONS

BMI, Body Mass Index

CHD, Coronary Heart Disease

CRP, C-reactive protein

CVD, Cardiovascular Disease

GI, Glycemic index

GL, Glycemic load

HDL, High-density lipoprotein

LCD, Low-calorie diet

LDL, Low-density lipoprotein

MetS, Metabolic syndrome

NHANES, National Health and Nutrition Examination Survey

RCT, Randomized Clinical Trial

RR, Relative Risk

T2DM, Type 2 Diabetes Mellitus

VLCD, Very-low-calorie diet

WHO, World Health Organization

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I. INTRODUCTION

1. Overweight and obesity

Overweight and obesity are a complex multifactorial conditions characterized by excessive accumulation and storage of body fat, increasing the risk of disease and decreasing the quality of life. Both conditions are usually determined by the body mass index (BMI), defined as an individual's weight in kilograms divided by the square of the height in meters (kg/m^2).

The World Health Organization (WHO) and National Institutes of Health defines overweight as having a BMI between 25 to 29.9 kg/m^2; and obesity as BMI greater than or equal to 30 kg/m^2 (1). Although BMI is a useful and easy measurement to assess overweight and obesity at a population level, it has several limitations (2). The most important limitation of this measure is that it doesn't take into consideration the degree of fatness of individuals. Athletic individuals, normally with higher percentage of muscle mass, may have a higher than normal BMI and yet have a normal percentage of body fat. In addition, there are different obesity phenotypes according the fat mass distribution in the body. Central or upper body distribution (android) has been more correlated with an increased risk of disease (3–5) than general, peripheral or bottom (gynoid) distribution.

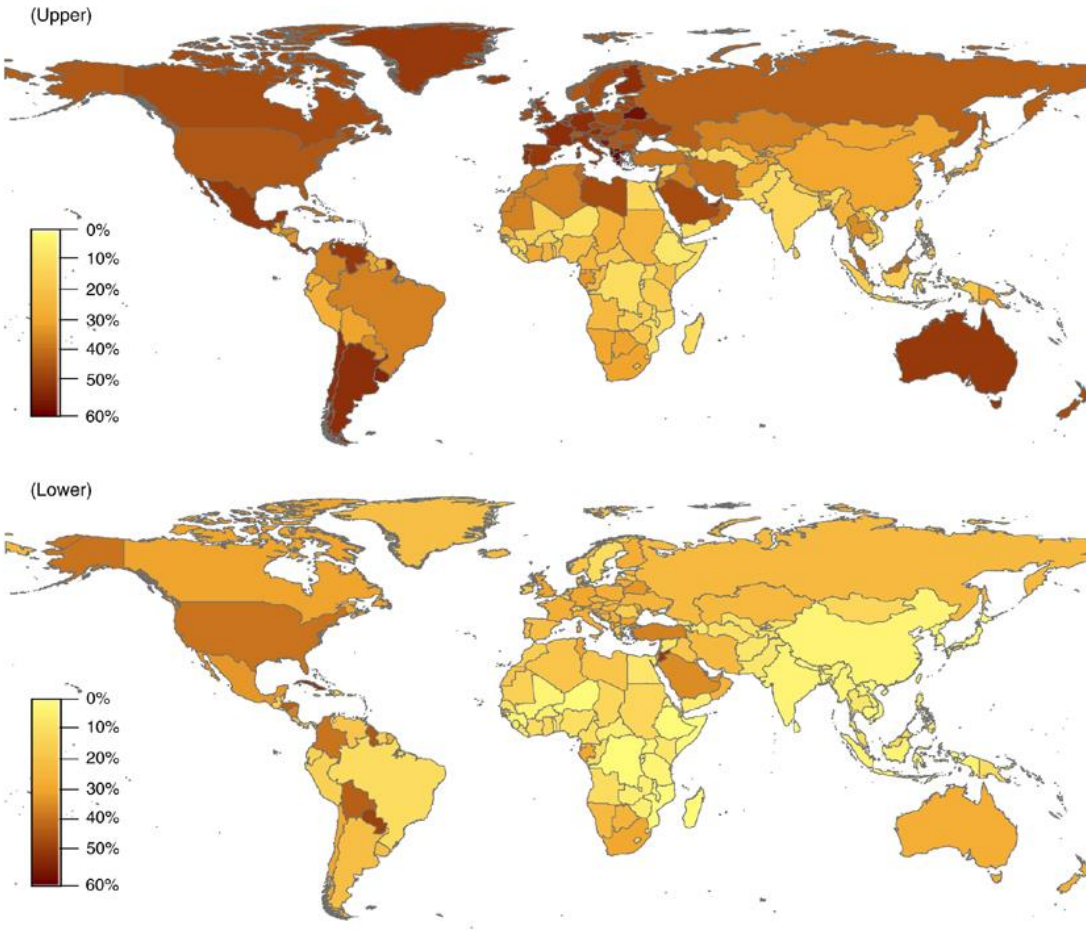
1.1 Prevalence and trends of overweight and obesity

Obesity has received a considerable attention as a major health problem and has reached epidemic proportion globally. This alarming increase affects both developed and developing countries throughout the world. At least 2.8 million people die as a consequence of being overweight or obese.

In the last 25 years, worldwide obesity prevalence has doubled. In 2008, the WHO estimated that 34% of men and 35% of women aged 20 or more were overweight; and 10% of men and 14% of women were obese (**Figure 1)**. With the current trend, by 2030 up to 58% of the world's adult population, approximately 3.3 million people, could be either overweight or obese (6). The

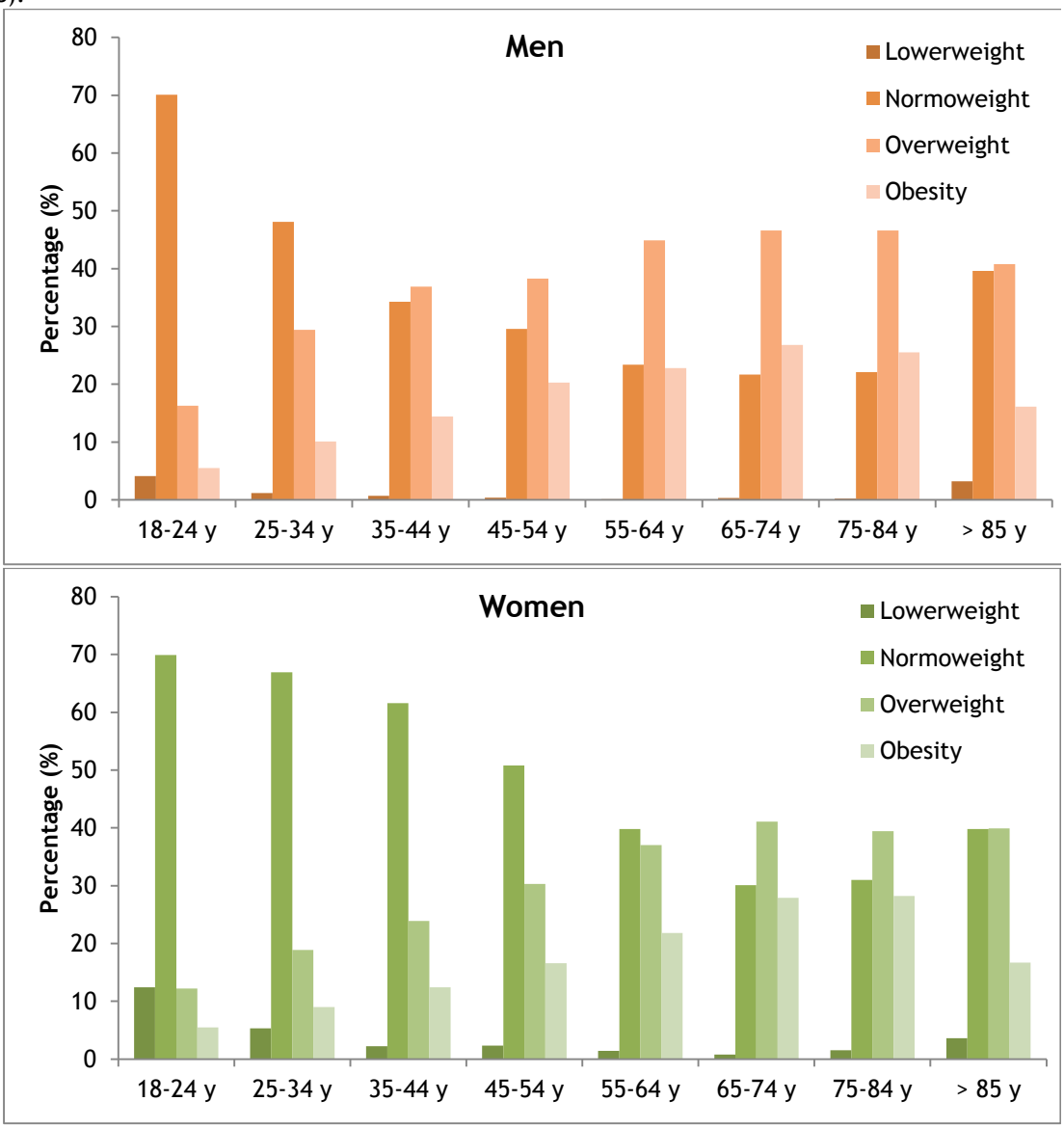
regions with highest prevalence of overweight and obesity were in the American and European regions (7). In the United States, 73 % of men and 66% of women have a BMI equal or greater than 25 kg/m^2. The prevalence in many European regions is also considerable, both northern (Germany and UK) and southern (i.e Spain and Greece). In UK, 66% of men and 58% of women could be considered overweight or obese (7).

Figure 1 Worldwide age-standardized prevalence of overweight (upper) and obesity (lower) in adults 20 years and older by country in 2005.



In Spain, overweight and obesity rates are particularly alarming with and especial increase in the incidence of the disease during the last 25 years.

Figure 2 Prevalence of overweight and obesity by age groups among Spanish men and women (8).



In 1987, 45% of men and 34% of the women had a BMI higher than 25 kg/m^2. The most recent data extracted from the national health survey of 2011-2012 estimates that 63% of men and 44% of women have overweight or obesity (**Figure 2**) (9).

Similar to adult, the prevalence in childhood obesity has been increased substantially over the last three decades (10). It has been estimated that 170 million children (aged less than 18 years) worldwide have overweight (11). An increase in BMI during childhood has also associated to serious health consequences and can be considered a risk factor for cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM) and cancer (12,13). These diseases not also generate premature mortality, but also long-term morbidity.

In USA, the prevalence of obesity has almost tripled among children and adolescents since 1980 (14). This data indicates that childhood obesity is increasing even more rapidly than adult obesity, suggesting major problems for the population's future health. A similar situation has been observed in Spain where nearly 30% of the children or adolescents are overweight or obese (9). Since 1987, the prevalence of overweight and obesity has increased 5% and 5,6% in boys and girls, respectively.

1.2 Obesity risk factors

Overweight and obesity are consequences of a disturbance in energy balance, when total energy intake (total amount of calories consumed) is higher than total energy expenditure (the combination of physical activity, basal metabolic rate and food thermogenesis). However, we still do not fully understand all underlying reasons of obesity because they are a complex mixture of genetic, environmental, psychosocial, cultural and cognitive factors.

1.2.1 Non-Modifiable factors

1.2.1.1 Genetic

Over the last 20 years, considerable strategies have been employed for the identification of genetic determinants of obesity, including studies of sever forms of obesity, genome wide linkage studies, candidate gene analyses and genome wide association studies.

During the eighties, twin and family studies suggested that 40-70% of the inter-individual variation in obesity risk and BMI can be attributed to genetic factors (15). Before 1995, the major attention in genetics of common obesity was candidate gene studies. Those studies were focused on genes with a suspected role in physiological pathways regarding body weight regulations and energy metabolism. One of the most studied is the melanocortin 4 receptor (*MC4R*) gene, widely expressed in the central nervous system. MC4R plays a key role in the regulation in food intake and energy metabolism. Functional mutations in *MC4R* are the commonest monogenic cause of sever early-onset obesity (16). However, in the past few years, genome wide association studies have led to breakthrough progress in the identification of obesity-susceptibly genes. To date, large-scale meta-analyses have identified 32 genetic loci associated with BMI, 14 loci associated with waist-to-hip ratio and 2 associated with percentage of body fat (17,18). Surprisingly, the combined effect of all-obesity associated variants is very modest and only explains 2% of the BMI heritability (19). The difference with the heritability of BMI estimated by twin and family studies (between 40% and 70%) could be partially explained by the modifying effects of environmental factors on genetic predisposition of obesity.

1.2.1.2 Gender/age/ethnicity

Gender, age and ethnicity are classical non-modifiable factors related to obesity. Gender differences in prevalence of overweight and obesity are no constant across regions or countries and sometimes are influenced by ethnicity and socioeconomic status.

Generally, epidemiological studies show that men have higher overweight and obesity prevalence than women in the majority of regions and countries, but not all of them. In USA, the gender difference in the combined overweight and obesity was small, as the prevalence in men (67.0%) was slightly higher than in women (62.0%), while fewer men than women were obese, 27.7% vs.

34.0% (20). On the contrary, in Spain, the prevalence of overweight was 45.2% in men and 28.2% in women, whereas obesity rates for men and women were 18% and 16%, respectively (8).

Significant age differences in the prevalence of overweight and obesity have been reported in various countries. In general, overweight and obesity prevalence is higher in adults than children in most countries. Part of the differences could be explained by the different diagnosis criteria used between children and adults (BMI vs. Age-sex-specific BMI percentiles), whereas others are actual differences due to age differences in physiology and health behaviors related to energy balance. Traditionally, prevalence of obesity has taken a "Λ" shape in relation to age. Several observational studies have found a gradual increase of obesity prevalence until 65 years of age, and a slightly decrease after that (21,22). Again, if we revise the data published in the last national health survey in Spain, similar trends were observed, although high obesity prevalence are carried around 75 years of age (9).

Ethnic differences among overweight and obesity prevalence have also been reported (20,23). Studies conducted in US populations have shown large differences in obesity prevalence between ethnic groups, especially among women. Data from the US National Health and Nutrition Examination Survey (NHANES) indicate that the prevalence of obesity was 30.2, 42.3 and 53.9% in white, Mexican American and black women, respectively (20).

1.2.2 Modifiable factors

Despite the role of non-modifiable determinants on weight gain, the epidemic proportions in obesity worldwide over the last 25 years cannot be explained by gender, ethnicity or genetic factors alone. The obesity epidemic is a reflection of changes in lifestyle, which have been too fast for our genes to adapt to (24,25). The increasingly obesogenic environment we live in is characterized by sedentary lifestyles, increased portion sizes, an abundance of energy dense, nutrient-poor, palatable foods that encourage overconsumption.

1.2.2.1 Physical Activity

Physical inactivity is one of the factors associated with the prevalence of overweight and obesity. A large cohort study in American nurses found that in 50,000 non-obese nurses, those who watched more television and had a sedentary lifestyle were at greater risk of developing obesity during 6 years of follow-up. The authors estimated that 30% (95%CI 24–36%) of new cases of obesity could be prevented by adopting a relatively active lifestyle (<10 h/week TV viewing and ≥30 min of brisk walking per day) (26). Also, the results of a multicenter prospective cohort study conducted in 23 centers in 10 European countries including 405,819 healthy volunteers showed a strong inverse association between total physical activity and BMI and waist circumference. Changing to one level of physical activity to another (Inactive, moderately inactive, moderately active and active) corresponded to a difference of 1 cm in waist circumference and to a difference of 0.25 kg/m2 in the BMI (27). In the last 2011-2012 Spanish Health National Survey, 59% of the participants performed light or no physical activity in the last seven days, and 35.9% of men and 46.6% of women declare themselves as sedentary (9).

1.2.2.2 Tobacco

Obesity and smoking are main causes of preventable morbidity and mortality around the globe (28). Smoking cessation have been associated with an increased risk of weight gain (29), due to a reduction in energy expenditure (30). However, the association between smoking and obesity is more complex. Several studies have found lower body weight and lower BMI among smokers than non-smokers (31). Smoking initiation in girls could be related to weight control (32), and among adult women, attempts for smoking cessation could be limited by fear of weight gain (33). In addition, smokers could also shear other obesity risk behaviors such as poor dietary habits and sedentary (34).

1.2.2.3 Diet

Several dietary factors have been associated with weight gain and a greater risk of obesity. Energy balance, food patterns and nutrient intake factors have been associated with body weight.

Energy density, obesogenic environment and food behaviors are determinants related to energy balance that the scientific community has focused their attention. Short term feeding trials have found that lower-energy dense food choices lead to a higher amount of food consumption but lower energy intakes compared to higher-energy density diets. An observational study, assessing whether dietary energy density predicts weight change over 6 y among a sample of non-Hispanic, white women, found that consumption of a lower-ED diet moderates weight gain. These results are supported by those observed in a randomized clinical trial (RCT) where 658 prehypertensive and hypertensive persons were randomly assigned to 1 of 3 groups: the established group received an intervention of 18 sessions implementing well-established hypertension recommendations, the established+Dietary Approaches to Stop Hypertension (DASH) group received an intervention of 18 sessions also implementing the DASH diet, and the advice group received 1 session on these topics. Authors concluded that both large and modest energy density reductions were associated with weight loss and improved diet quality. This suggests that lower-energy density diets may lead to better appetite regulation and improved body weight control (35–37). In line with these results, some investigators have pointed out that portion size of foods as other contributing factor of weight gain. Current scientific evidence shows that the portion size of foods are related to the amount of food intake, and also to the perception of the individuals towards food (38). Other factors such skipping breakfast or snaking have also been associated with weight gain, however the results are controversial and inconsistent (39).

The so-called obesogenic environment is also a determinant factor that contributes to increase the prevalence of obesity. The absence of supermarkets in local neighborhoods, principal source of vegetables and fruits, and long distance to supermarkets are associated with higher BMI (40–42).

Additionally, moderately strong evidence now indicates that some dietary patterns, including Mediterranean diet or Vegetarian diet, could play a role in the prevention of overweight and obesity (43,44). Mediterranean diet, characterized by a high intake of olive oil, fruit, nuts, vegetables, and cereals; a moderate intake of fish and poultry; a low intake of dairy products, red meat, processed meats, and sweets; and wine in moderation, consumed with meals, has been

inversely associated with BMI and obesity (45–54). The results of an observational study conducted in 3162 Spanish men and women aged 25–74 y showed that increasing adherence to the traditional Mediterranean dietary pattern reduced the obesity risk. Those individuals in the highest tertile of Mediterranean diet adherence had a 40% less risk to be obese than those in the lowest (47). Vegetarian diet has also been proposed as a valid dietary pattern for the prevention of obesity. Several observational studies have evaluated the associations between vegetarian diet and BMI (44,55–58). All of them found that those individuals who followed a vegetarian diet had a lower BMI, than those who followed an omnivore diet. Rosell et al., conducted a prospective cohort study to evaluate 5-year changes in body weight among the participants of the EPIC-Oxford study. The authors categorized 21,966 healthy adults in 6 groups: meat-eating, fish-eating, vegetarian, vegan, reverted and converted. Those who during the follow-up period had changed their diet in one or more steps in the direction vegan > vegetarian > fish-eater > meat-eater, were classified as 'reverted' and subjects who had changed their diet by one or more steps in the opposite direction were classified as 'converted'. Among those who did not change their diet, meat-eaters were those with more weight gain, whereas among those who changed their diet, converted had the lowest weight gain and reverted the highest (44).

Finally, some nutrients and specific foods have also been associated with body weight. Dietary fat is the macronutrient with the highest energy content; however it exerts a weak satiating effect. Thus, it has been suggested that high-fat diets could be associated with weight gain due to the poor satiating effect of dietary fat that could lead to overconsumption. Evidence from epidemiologic studies linking fat intake to weight gain or obesity is weak (59–61) and inconsistent (62–68). The results from the Nurses' Health Study among 41,518 women reported weak positive associations between total fat intake and weight gain over 8 years, although there was a strong positive association with the percentage of energy from animal fat, saturated fat, and trans fat (69). On the contrary, Forouhi et al. didn’t found a significant association between the amount or type of dietary fat and subsequent weight change in 89,432 men and women from 6 cohorts of the European Prospective Investigation into Cancer and Nutrition study (70).

Dietary carbohydrates have also been associated with body weight and obesity. The majority of epidemiological studies evaluating the associations between carbohydrates intake and measures of overweight and obesity (BMI and waist circumference) have shown and inverse correlation (71–82). Carbohydrate intake was found inversely associated with body weight gain in a cohort of 376 Danish men and women (81). Higher carbohydrate intake was also associated with lower risk of obesity among 63,307 United States women in the Cancer Prevention Study II Nutrition Cohort (82).

The role of dietary protein on body weight is highly controversial. Owing to the high satiating effect of dietary protein, it has been suggested that high-protein diets could be associated to a decreased energy intake. However, there is not sufficient evidence to support this theory (83–89). Current scientific evidence suggests a differentiated role of dietary protein depending on the source (animal or vegetal). Kahn and coworkers evaluated changes in BMI and waist circumference in a cohort of 29,236 adults with a follow-up of 10 years. Increased BMI was positively associated with meat intake (89). In 2010, Vergnaud et al., evaluated the association between meat intake (red meat, poultry and processed meat) and weight gain in 270,348 women and 103,455 men during 5 years of follow-up. After controlling for potential confounders, the authors found a positive association between meat consumption and a higher BMI (88).

Dietary fiber has been related with several health benefits, including body weight management by several mechanisms. Cross-sectional prospective studies have associated dietary fiber intake with a lower weight gain (90–92). This association has also been observed in longitudinal studies (93–97). Koh-Banerjee et al., showed that the increase in dietary fiber coming from fruit and whole-grain cereals was inversely associated with weight gain at long-term in a cohort of 27,082 adult healthy men (97).

Dietary glycemic index (GI) and glycemic load (GL) has also been associated with BMI and obesity, however it will be examined in a subsequent section.

1.3 Obesity as a risk factor

Obesity is an important risk factor of hypertension, T2DM, dyslipidemia, CVD and some types of cancer (98) (98), increasing the risk of mortality and decreasing quality of life.

1.3.1 Hypertension

It is estimated that at least 75% of the incidence of hypertension is related directly to obesity (99). Experimental animal studies have demonstrated a consistent rise in blood pressure with excess weight gain induced by prolonged high fat diet (100,101). Epidemiological data unequivocally support the link between body weight and BP. Data from the NHANES indicates that the prevalence of hypertension among obese individuals was 42.5% compared with the 27.8% for overweight individuals and 15.3% for those with normal BMI (102). Additionally, higher BMI is also associated with greater risk of having hypertension. In the Framingham Heart Study, compared to those individuals with normoweight, the relative risk of developing hypertension in long-term follow-up were 1.48 and 1.70 for overweight men and women and 2.23 and 2.63 for obese men and women, respectively (103). Clinical studies also suggest that excess weight gain is a key contributor to elevated blood pressure in most patients with primary hypertension. Weight loss between 5%-10% decreases blood pressure in normotensive as well as in hypertensive obese subjects and reduces the need for antihypertensive medication (104).

Mechanisms underlying the link between obesity and hypertension include the renin-angiotensin-aldosterone system , the sympathetic nervous system (SNS), metabolic dysregulation (including hyperinsulinemia, adipokine imbalance, and increased inflammatory cytokines). Activation of renin-angiotensin-aldosterone system system thought basically the SNS is a major factor of the obesity-related hypertension (105). Insulin and Leptin, both increased in individuals with obesity (106), have also found to activate the SNS (107) and, therefore, contribute to obesity-related hypertension. I addition, insulin has direct effect on sodium retention in the kidney (108). Another contributing factor in obesity-associated hypertension is vascular stiffness which is influenced by adipokines such as leptin and hyperinsulinemia (109).

1.3.2 Type 2 diabetes mellitus

The prevalence of T2DM and Obesity are both increasing exponentially. Evidence from epidemiological studies show that obesity and weight gain are associated with an increased risk of diabetes (110,111). BMI, waist circumference and hip-to-waist ratio are anthropometric measurements used as risk indicators for T2DM (112,113). Recently, a meta-analysis of 15 prospective studies has found that waist circumference and waist-to-hip ratio (markers of abdominal obesity or visceral fat) could be better indicators of T2DM risk than BMI (marker of general obesity) (114).

Obesity-induced T2D has been recognized as an inflammatory disease. The systemic low-grade inflammatory response that is often observed in obesity detrimentally affects both insulin signaling and beta-cell function and may thus contribute to the development of T2D (115–117).

1.3.3 Cardiovascular Disease

Cardiovascular disease is caused by disorders of the heart and blood vessels, and includes coronary heart disease (myocardial infraction), cerebrovascular disease (stroke), raised blood pressure (hypertension), peripheral artery disease, rheumatic heart disease, congenital heart disease and heart failure. Now a days, CVD are the leading cause of mortality in developed countries (118) and it is estimated that it will increase, especially in low and middle income countries (119).

As stated before, obesity is a precursor of hypertension, diabetes and their associated risks, and, therefore a risk for CVD. Epidemiological evidence have shown a positive association between overweight and obesity, and coronary heart disease (CHD) and stroke (120–122). Data from a meta-analysis including 21 cohort studies with more than 300,000 participants showed a significant increased risk of CHD independently of traditional risk factors (blood pressure and cholesterol concentrations). Relative Risk (RR)s (95% CI) for moderate overweight and obesity compared with normal weight were 1.32 (1.24-1.40) and 1.81 (1.56-2.10), respectively (122). In case of stroke, another meta-analysis of prospective studies with 2 million participants showed significant direct and graded association between excessive body weight and ischemic stroke.

After adjusting for potential confounders, RR (95% CI) for ischemic stroke was 1.22 (1.05–1.41) for overweight and 1.64 (1.36–1.99) for obesity (120).

1.3.4 Cancer

Epidemiological estimations shows that 20% of all cancers are caused by excessive body weight (123). In postmenopausal women, in particular, approximately 50% of all cancers can be attributed to obesity (124). Many prospective epidemiological studies have demonstrated a positive association between overweight and cancer, even though obesity alone does not apparently heighten cancer risk in all tissues by the same amount (12,123–128).

A recent systematic review and meta-analysis of prospective observational studies, with 282,000 incident cancer cases and a follow-up greater than 133 million person-years, has demonstrated that the obesity and cancer association is sex specific over a wide range of malignancies, and this remains mostly true for different geographic populations (125).

The reports of international agencies for cancer research have showed that most common types of cancer in obese individuals are endometrial, esophageal adenocarcinoma, colorectal, postmenopausal breast, prostate, and renal (12,128).

Apart of from BMI, other anthropometrical measurements including waist circumference or waist-to-hip ratio have been investigated as adiposity indicators of cancer risk. Several cancers, such as colon, premenopausal breast, endometrium, and esophageal adenocarcinoma, together with pancreas tumors, have been more associated with abdominal obesity than BMI (129–133).
Due to the great variety of cancers associated with abdominal and general obesity, the list of possible mechanisms linking both pathologies is also extensive. Lifestyle, genetic and molecular factors have been related obesity to cancer (134–141).

2. Metabolic Syndrome

2.1 Pathology and diagnose

The metabolic syndrome (MetS) was used, simultaneously, for the first time at the end of the seventies by Haller (142) and Singer (143) to describe different combinations of metabolic disorders such as central obesity, diabetes mellitus, hyperlipoproteinemia, hyperuricemia, hepatic steatosis, gout and hypertension. In 1988, this concept, also called insulin resistance syndrome (144), was unified by Reaven (145), although obesity was not present in this definition. Now a day, the MetS is defined as a cluster of several cardiometabolic risk factors including central obesity, hyperglycemia, hypertension and atherogenic dyslipidemia. This term was officially institutionalized by the WHO (146) and the Third Report of the National Cholesterol Education Program's Adult Treatment Panel (ATP III) (147,148). Additionally, similar, but not equal, definitions were described by other institutions (149–151).

In 2009, an unique definition was established by the International Diabetes Federation and American Heart Association/ National Heart, Lung, and Blood Institute (152). They agreed that the presence of any 3 of the 5 risk factors constitutes a diagnosis of MetS. In **Table 1** are shown the 5 criteria used for its definition.

Table 1 Criteria for Clinical Diagnosis of the Metabolic Syndrome(152).

Measure	Categorical Cut Points
Abdominal Obesity	Population- and country-specific definitions
Elevated triglycerides	≥150 mg/dL (1.7 mmol/L) or drug treatment
Reduced HDL-C	<40 mg/dL (1.0 mmol/L) in males; <50 mg/dL (1.3 mmol/L) in females or drug treatment
Elevated blood pressure	Systolic pressure ≥130 mmHg and/or diastolic pressure ≥85 mmHg or drug treatment
Elevated fasting glucose	≥100 mg/dL or drug treatment

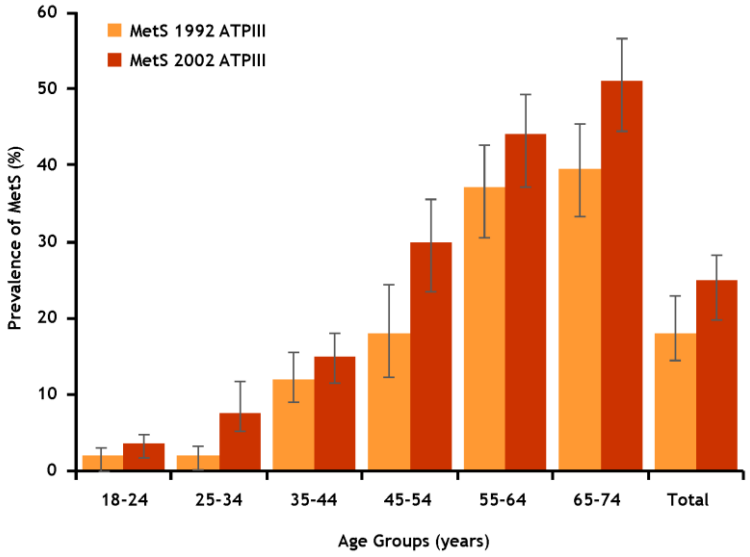
2.2 Prevalence and trends of Metabolic Syndrome

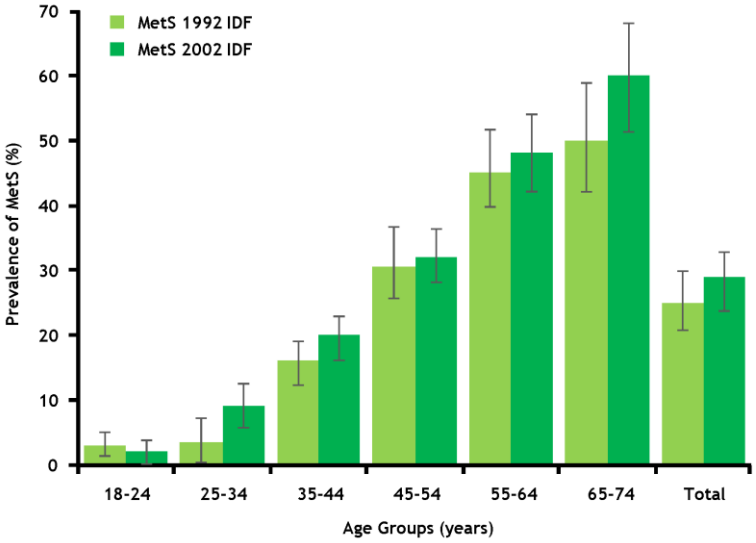
Like the obesity epidemic, the MetS has become one of the major health problems worldwide. It is estimated that the prevalence of the MetS among worldwide adult individuals is reaching 25% of the population (153–156).

In the U.S., approximately one-fifth of the adult population is at high cardiovascular risk (154,155). Data from the NHANES indicates that, between 2009 and 2010, the age-adjusted prevalence of MetS in adult population was 22.9% (95% CI: 20.3% to 25.5%). The same authors found a slightly decrease in the prevalence of the MetS between 1999 [25.5% (95% CI: 22.5% to 28.6%)] and 2010 [22.9% (95% CI: 20.3% to 25.5%)] due to a decrease in hypertriglyceridemia prevalence (33.5% to 24.3%), as did elevated blood pressure (32.3% to 24.0%) (155). They suggest that the decrease in hypertriglyceridemia and hypertension is correlated with an increase in in lipid-modifying and anti-hypertensive drugs, respectively.

Similar situations have been observed in several European countries. A study with 11 European and one US population-based cohorts found that almost 25% of the adult population had MetS. They also found that the prevalence increased with advanced age, from 3.7 with age between 20 and 29 years to over 30% with age 70 years or more.

Figure 3 Prevalence of metabolic syndrome in the periods 1992–1993 and 2002–2003 (157).





Countries with a higher prevalence of MetS were Lithuania (>60%), Greece (40%) and Spain (40%), whereas those with lower prevalence were Italy (Sardinia) (<10%), Sweden (>10%) and Belgium (<20%). In the Mediterranean population of Catalonia, Spain, the prevalence of MetS between 1992 and 1993 were 18.4% (95% CI 15.8–21.1%) using the ATPIII criteria and 25% (95% CI 22.0–28.0%) with IDF. After 10 years, the prevalence had increased a 6.4% when ATPIII criteria were used and a 3.5% when IDF criteria were used (**Figure 3**) (157).

2.3 Metabolic Syndrome as a cardiovascular risk factor

As stated before, the MetS is a cluster of CVD risk factors and therefore, it is reasonable to thing that those individuals with MetS could be more exposed to develop CVD. Many studies have evaluated the associations of prevalence of MetS and risk of CVD (158–165).

In a recent meta-analysis of 87 prospective observational studies which included nearly one million men and women with a mean follow-up of ranging from 1.0 to 32.7 years, Mottillo et al. investigated the associations of MetS and risk of CVD, CVD mortality, stroke, myocardial infarction and all-cause mortality (158). They found that the MetS was associated with and

increased risk of CVD (relative risk [RR]: 2.35; 95% CI: 2.02 to 2.73), CVD mortality (RR: 2.40; 95% CI: 1.87 to 3.08), all-cause mortality (RR: 1.58; 95% CI: 1.39 to 1.78), myocardial infarction (RR: 1.99; 95% CI: 1.61 to 2.46), and stroke (RR: 2.27; 95% CI: 1.80 to 2.85). They also found that RR for all estimates of cardiovascular risk was slightly higher in women than men, especially in all-cause mortality.

The pathophysiological mechanisms linking the MetS with an increased risk of CVD is still unknown (152). However, it is largely accepted by the scientific community that insulin resistance is an underling process of the MetS. Insulin resistance, represented by hyperinsulinemia and hyperglycemia, lead to the activation of the sympathetic nervous system triggering sodium retention and volume expansion and, thus, higher BP (166,167). Also, hepatic production of very low-density lipoproteins is increased in those individuals with insulin resistance, leading to hypertriglyceridemia, low High Densisty Lipoprotein (HDL) cholesterol, elevated apolipoprotein B, elevated small Low Density Lipoprotein (LDL) cholesterol, and consequently, atherosclerosis (168–170).

3. Treatment of Obesity and Metabolic Syndrome

The main goals of Obesity and MetS treatment include sustained weight loss with a primary focus on abdominal obesity, improvement of obesity-related health risks and quality of life, and reduction of mortality. Intentional weight loss normally is associated with reduced mortality, improved blood pressure and lipid profile, mental health and quality of life (171). A modest weight loss of 5-10% significantly reduces obesity-related risks (171,172).

Mainly, there are three strategies for obesity treatment. Bariatric surgery can be considered for patients with more severe disease and who meet its indications. Pharmacotherapy may be useful in some individuals for whom non-pharmacological approaches alone are ineffective or insufficient. However, lifestyle management, including diet and physical activity, is recommended as the first-line treatment for obesity and its metabolic consequences.

3.1 Surgical treatment

The International Federation of Surgical Obesity has in consideration several selection criteria which make a patient suitable for bariatric of weight-loss surgery. Patients must have a BMI ≥ 40 kg/m^2 or those with a BMI ≥ 35 kg/m^2 who have associated high-risk comorbid conditions such as atherogenic diseases, or T2DM; reasonable attempts at other weight loss techniques; age between 18-65 years; obesity related health problems; no psychiatric or drug dependency problems; a capacity to understand the risks and commitment associated with the surgery and pregnancy not anticipated in the first two years following surgery.

Traditionally, bariatric surgery has been classified in three categories based on anatomical changes, restrictive, restrictive-malabsorptive and malabsorptive. However, clinical benefits of bariatric surgery in weight loss and improving metabolic comorbidities have been attributed to changes in the physiological responses of gut hormones and adipose tissue metabolism (173,174). The most common techniques performed in bariatric surgery are Laparoscopic Adjustable Gastric Banding, Laparoscopic Sleeve Gastrectomy and Roux-en-Y Bypass. Mean percent weight loss is estimated to be between 25% to 95% of total excess weight, depending on the procedure (175).

Several studies have demonstrated a decrease in co-morbid conditions and improvement in health after surgery for obesity (176–178). Data from the Swedish Obese Subjects study showed a decrease in prevalence of cancer and a 28% reduction in the adjusted all-cause mortality rate in those subjects in the surgical group compared with conventionally treated obese (177,178). Data from 7,925 patients of the Utah study also supports these results showing a 52% lower rate of death from all-causes (176).

3.2. Pharmacological treatment

Improving diet combined with reinforced physical activity constitutes the first-line management for overweight or obesity, but adherence to lifestyle measures is difficult to achieve. Individuals who cannot achieve significant weight loss by lifestyle interventions alone may benefit from pharmacological agents which promote weight loss.

Weight loss medications have been classified in two major categories: appetite suppressants and gastrointestinal fat blockers. Appetite suppressing medications have targeted three monoamine receptor systems in the hypothalamus: noradrenergic, dopaminergic and serotonergic (179). In the other hand, Orlistat is a potent slowly reversible inhibitor of pancreatic, gastric, and carboxylester lipases and phospholipase A2, which are required for the hydrolysis of dietary fat in the gastrointestinal tract into fatty acids and monoacylglycerols (180).

Orlistat, lorcaserin, and phentermine plus topiramate-ER, the most used weight-loss drugs at this time, increases the chances to achive a >5% of weight loss after 1 year when are used in conjunction with lifestyle intervention (181). However, in Spain, Orlistat is the only accepted pharmacological treatment for obesity.

3.3. Lifestyle modification

The key element of obesity treatment is assisting patients to develop healthy lifestyle habits through the improvement of better dietary and physical activity choices that will lead to a gradual weight loss. The initial goal is to achieve a 5% to 10% weight loss over the initial 6 months of treatment (182). Caloric restriction is the most important component in achieving weight loss, focusing in fat mass, whereas increased and sustained physical activity is particularly important in maintaining the lost weight and reducing the loss of fat free mass (183–185).

3.3.1 Physical activity

It has been well established that weight control is a delicate balance between energy intake and energy expenditure, of which energy physical activity is the most variable and modifiable component of the energy expenditure side of the energy balance equation. Physical activity is ranged between 10% and 40% of total daily energy expenditure and thus plays an important role in the treatment of overweight and obesity (186). The American College of Sports Medicine recommends 150 to 250 minutes per week to prevent weight gain(187) and 225 to 420 to promote clinically significant weight loss (183).

Epidemiological data suggest that physical activity is a key element in weight gain (186,188–190). Data from 9325 individuals of NHANES showed that low levels of self-reported recreational physical activity were associated with a 3-fold and 5-fold increased risk of weight gain in men and women, respectively (191).

However, the results obtained from studies investigating weight loss as a result of aerobic exercise training are very heterogonous. The Dose Response to Exercise in Women study found no significant changes in body weight in 464 postmenopausal women exercising at 50% (− 0.4 kg), 100% (− 2.2 kg) and 150% (− 0.6 kg) of public health guidelines for 6 months despite greater than 89% adherence in all ET groups. Also, the Inflammation and Exercise study (n=129) observed no significant weight loss after 4 moth of exercise training (-0.4 kg) compared with the control group (0.1 kg) (192). On the contrary, the Diabetes Aerobic and Resistance Exercise study showed significant weight loss in the exercise training group (-0.74 kg) compared to the control group after 22 weeks of intervention in 251 adults with T2DM.

Although approximately >2 kg can be achieved by exercise training alone, most studies of short-term weight loss interventions show that the most significant weight loss occurs when a combination of diet and exercise is used (183,193–195).

3.3.2 Diet

Dietary treatment of obesity has as a primary objective to achieve a sustained weight loss which allows decreasing obesity-related risks to health. During the last decades, numerous attempts have been done to deal with obesity.

The majority of the international societies studying obesity recommend low-energy diets as the most valid approximation to obesity treatment (196–204). Although low-energy diet has not a specific definition, scientific community and health professionals have established low-energy diets as diets with a reduction between 500 and 1000 kcal/d of daily calorie needs and with a

total energy intake greater than 800 kcal/d. Macronutrient composition of the low-calorie diet (LCD) is still a matter of debate, although a standard composition for a well balance diet has been proposed (**Table 2**) (197). The use of this type of diets, with a treatment period between 6 and 12 months, has been associated with a mean loss of about 8%, although, with longer periods (3-4.5 years), the loss decreases to about 4% (205). To achieve the calorie reduction, several strategies have been proposed including low energy density foods, meal replacements and portion size.

Some studies have evaluated the effect of energy density of foods as obesity treatment (206-209). Ello et al. conducted a 1-year randomized controlled trial to evaluate the effect on weight loss of 2 strategies, one low-fat group and one low-fat group + low energy density foods, for reducing the energy density of the diet. After one year, both groups had significant weight loss, although low energy density foods group had significantly higher loss (209).

Table 2 Recommended macronutrient composition for treatment of obesity(197).

Energy	Percentage
Carbohydrates	45-55%
Proteins	15-25%
Lipids	23-35%
Saturated Fatty acids	<7%
Monounsaturated Fatty acids	15-20%
Polyunsaturated Fatty acids	<7%
Trans Fatty acids	<2%
Fiber	20-40g

One of the most important factors which affect weight-loss diets is the treatment adherence. A suggested strategy to facilitate diet adherence has been to use meals replacements. Meal replacements products have also been shown to improve weight loss (210,211). In 2003, Heymsfield et al, conducted a meta-analysis including 6 randomized controlled clinical trials with

487 participants and a follow-up between 3 and 51 months. A significant higher weight loss was observed in the group using meal replacements (7% loss of the initial body weight) than the control group (4% loss of the initial body weight). Meal replacement has also been investigated as nutritional strategy for weight maintenance. A randomized controlled trial was conducted to assess the long-term effects of 2 energy-restricted diets on weight loss in 100 participants. During the first 3 months, one of the intervention groups replaced 2 of the 3 meals with meal-replacement shakes, soups or hot chocolate. During this initial phase, the meal-replacement group lost 11.3+/-6.8%, whereas the control group lost 5.9+/-5.0% (210). In a second phase of the same study, both groups were prescribed the same energy-restricted diet with one meal and one snack replacement for an additional 4 year to maintain the weight loss. At the end of follow up, both groups maintained the initial weight loss and average weight loss of meal-replacement group was consistently greater than control group ($p = 0.001$).

Portion size is an important determinant of energy intake. The number of calories ingested by subjects at a meal has been directly correlated with the serving size offered (212,213). A 6-month clinical trial evaluating the effect of portion size vs. usual care in 130 obese individuals found that those individuals in the intervention group loss more weight than those in the control group (mean ± SD, 1.8% ± 3.9% vs 0.1% ± 3.0%, $P = .006$) (214). Larger studies are needed to assess the utility of portion size tools in obesity treatment.

A similar approximation to low-energy diets are very-low-calorie diets (VLCD). VLCD are commercially formula foods, providing about 450–800 kcal/d, replacing all meals and snacks. The use of this type of diets are reserved for patients with severe obesity (BMI ≥ 30 kg/m^2) (215) and should only be used for fewer than 16 weeks because of clinical adverse effects (216). Scientific evidence regarding VLCD suggest that this type of diets is not more effective at long-term than conventional low-calorie diet (203). The majority of the studies found that participants who completed a comprehensive VLCD program (that included lifestyle modification) generally lost 15% to 25% of initial weight in 3 to 4 months (217–223) in comparison to the 8% achieved with the LCD. In a meta-analysis of 6 RCT including 425 morbidly obese participants with a follow-up

between 6 to 26 months, Tsai et al. found that, compared with the LCD, VLCD generated a higher short-term weight loss (9.7± 2.4% vs. 16.1±1.6%, respectively; P = 0.0001), although similar long-term weight losses were found between the two type of interventions (5.0 ± 4.0% vs. 6.3 ± 3.2%, respectively; P > 0.2) (223).

Calorie restriction can achieve a moderate amount of weight loss in a short term basis, but often this dietary induced weight-loss cannot be maintained long term (205). A large number of dietary strategies with different proportions of lipids, proteins, and carbohydrates are currently being investigated. There is an intense debate about the different diets and macronutrient proportions that are most effective for treating overweight or obesity. Several trials assessing dietary composition have been conducted to improve both weight loss and weight maintenance.

3.3.2.1 Low-fat diets

Over the last 30 years, high-carbohydrate, low-fat diets are recommended as 'healthy' for the population in general (224) as well as for individuals susceptible to heart disease (225), cancer (226), hypertension (225,227), and diabetes (228). Traditionally, low-fat diets have been the primary approach of the dietary intervention for obesity treatment (197,201,202,204). There are several reasons for targeting dietary fat intake (229,230). Compared with carbohydrates and proteins, fat is the most concentrated source of energy, providing ≈38 kJ g^{-1} as opposed to 17 kJ g^{-1} for carbohydrate or protein, and is preferentially stored in adipose tissue (231). High-fat foods are relatively less satiating than are isoenergetic portions of high-carbohydrate or high-protein foods; thus individuals on a high-fat diet would tend to consume more total energy to gain the required amount of carbohydrate as someone on a low-fat diet (232). Furthermore, the improved taste and palatability of fatty foods increase the potential for active overconsumption.

Several clinical trials have evaluated the effect of energy-restricted low-fat diets on weight loss. A multicentric intervention trial evaluated whether an energy-restricted low-fat diet (25%) was superior to an energy-restricted moderate high-fat diet (40%) for the treatment of obesity. At the end of the intervention, average weight loss was 6.9 kg in the low-fat group and 6.6 kg in the

high-fat group (p>0.05). However, more subjects lost >10% in the low-fat group than in the high-fat group ((20.8%, n = 70) versus (14.7%, n = 46) (P = 0.02) (233). Powell et al conducted a clinical trial with thirty-five obese women 25 to 45 years of age where randomly allocated into one of four energy- restricted dietary fat groups, with 10%, 20%, 30%, or 40% of caloric intake as dietary fat. After 12 weeks, no significant differences in the rate or amount of body weight or percent body fat lost across the four groups (234).

3. 3.2.2 Hyperproteic diets

Now a days, hyperproteic diets, based on carbohydrates substitution for protein, has become a popular alternative due to the potential benefits for obesity treatment. Traditionally, dietary recommendations for protein intake has been established around 10-15% of the total energy intake, however, the protein intake of actual hyperproteic diets is around 20-30%. Among the most popular hyperproteic diets there are the Atkins diet, the Zone diet and most lately the Dukan diet. Although these type of diets have become extremely popular among general population, scientific community have not yet reach a clear opinion either hyperproteic diets are a good alternative for body weight or not.

Short-term clinical trials assessing the effect of high-protein intake have found a modest positive effect on weight loss, although this beneficial effect is not sustained in a long term basis (197). A recent meta-analysis of 24 RCT evaluated energy-restricted, isocaloric, high-protein, low-fat diets with standard-protein, low-fat diets on weight loss, body composition, resting energy expenditure, satiety and appetite, and cardiometabolic risk factors. The authors found a moderate beneficial effect of high-protein, low-fat diets on weight loss at short-term on comparison of standard-protein, low-fat diets [mean difference, 95% CI: -0.79 kg (-1.50, -0.08), P=0.03, respectively). Also, in comparison to standard-protein, low-fat diets, high-protein, low-fat diets had greater reductions in fat mass (−0.87 kg; 95% CI: −1.26, −0.48 kg), in fat-free mass (0.43 kg; 95% CI: 0.09, 0.78 kg) and resting energy expenditure (595.5 kJ/d; 95% CI: 67.0, 1124.1 kJ/d) (235). Despite the moderate beneficial effects at short-term, RCT comparing high-protein diets vs. standard diets didn't achieve to replicate the same results at long-term (236–242). Only

the study of Gardner et al. compering 4 different diets (Atkins, Zone, Ornish y LEARN) found significant greater body weight reductions among those in the Atkins diet (low-carbohydrates and a 27% of protein content) than the rest of intervention diets (243). However, the study was only conducted in women (n=311) and the rest of the intervention diets were not traditional high-carbohydrates diets but different popular diets.

One of the major concerns about high-protein diets was their long-term safety (244). In 2007 two prospective observational studies were published evaluating the associations of protein consumption and cardiovascular and all-cause mortality. The first study was conducted in 42,237 Swedish women, with a mean follow-up of 12 years, where those individuals with higher protein and lower carbohydrate intakes had a 37% more risk of cardiovascular death and an 11% more risk of all-cause mortality (245). Similarly, the authors of the second study, conducted in 22,944 Greek adults (mean follow-up of 10 years), found that also those participants in with higher intake of carbohydrates and protein had an increased risk of all-cause mortality (per 5 units, HR: 1.22; 95% CI 1.09 to 1.36) (85). However, some authors suggests that protein source could be a key element in the associations between protein intake and mortality (84,246).

3.3.2 3 Low-fat vs. Low-carbohydrate diets

Although international institutions and public health guidelines promote high carbohydrates, low fat, energy-restricted diets as the first option for obesity treatment, the persistence of obesity epidemic have been increasing for the last decades and new dietary strategies have to be evaluated to overcome this epidemic.

Low-carbohydrates diets have been proposed as a valid alternative to low fat-diets. The logic explanation to carbohydrate restriction is that, in response to postprandial hyperglycemia, changes in regulatory hormones, insulin and glucagon, will increase fat oxidation and decrease fat storage.

A great number of trials and several meta-analyses have compared the effects of low-fat diets vs. low-carbohydrates diets on weight loss (247–250). In 2006, two similar meta-analyses of RCT were published comparing the effects of low-carbohydrates diets vs. low fat diets (248,249). First, Nordmann et al. published a meta-analysis of 5 RCT compering low-carbohydrates diet without caloric restriction vs. energy-restricted low-fat diets. The results showed that low-carbohydrates diets exert a greater weight loss than low-fat diets during the first 6 months, although this effect was not significant at 12 month. Similar results were found in another meta-analysis of 6 RCT conducted by Levine and coworkers. The authors conclude that low-carbohydrates diets resulted in a higher weight loss than low-fat at 6 months

4. Glycemic index and glycemic load

4.1 Glycemic index

The concept of the GI was derived from the dietary fiber hypothesis proposed by Burkitt and Trowell, who suggested that foods with a slow absorption rate could have better metabolic benefits in relation to western societies' diseases such diabetes and coronary heart disease (251). The origin of the GI concept was to establish a valid and robust measure to calculate the impact of the carbohydrates present in foods on blood glucose concentrations. In 1981,Prof David Jenkins and coauthors defined the GI concept as the incremental area under the blood glucose response curve of a 50g carbohydrate portion of a test food expressed as a percent of the response to the same amount of carbohydrate from a standard food taken by the same subject (252). Thus, the GI is a property of the carbohydrates present in the foods, and it's determined by several factors including the nature of the monosaccharide forming the carbohydrates, the amount of carbohydrates absorbed and the amount that are metabolized. The methodology for GI calculation is recognized and described by the International Standards Organization (26 642:2010) and by the Food and Agriculture Organization of the United Nations (253). Intrinsic and extrinsic factors that alter the rate of gastrointestinal motility, digestion and absorption, and the nature of the starch, cooking method, particle size, and the presence of fiber, fat, and proteins were all found to result in differences in the GI (254,255). Although the glycemic response generated

by these foods could differ between individuals with different metabolic conditions, the GI of foods is very similar regardless of the pathophysiological condition of the individuals (256). The GI of a diet can be calculated through the individual GI values of the foods composing the whole diet, and it can estimate the quality of the dietary carbohydrates regardless of the amount consumed (257).

Due to glycemic responses generated by carbohydrates are strongly related to insulin responses (258,259), GI has been investigated as a possible tool for the prevention or treatment of chronic diseases (260–262). GI was firstly used as a dietary tool to T2DM management, however subsequent studies have associated GI with other chronic diseases such CVDs, cancer and obesity with inconsistent results.

Several investigators have suggested that hyperglycemia generated by high-GI diets can be a key dietary factor in the pathogenesis of the T2DM. Prospective cohort studies have found strong positive associations between GI and risk of T2DM incidence (263–267). A recent meta-analysis of 21 prospective cohort studies has evaluated a systematic literature review and dose-response meta-analysis of evidence from prospective cohorts. The results of this recent meta-analyses indicated significant a dose-response RR for GI (1.08 per 5 GI units; 95%CI: 1.02 to 1.15) (268).

Also, several RCT have evaluated the effect of dietary GI as a dietary approach to the treatment of T2DM. Ajala et al. published a systematic review and a doses-response meta-analysis of RCT evaluating the effect of GI on the overall strategy of diabetes management. Beneficial effects on glycated hemoglobin was found on those individuals allocated in a low-GI versus other diets (high-GI, high fibre or American Diabetes Association recomendations) (Mean difference: -0.14; 95%CI: -0.24, -0.03, respectively) (269).

Postprandial state has been recognized as a key point on the development of cardiovascular risk factors. Elevated postprandial glycemia and insulinema present after the consumption of high-GI foods are two important risk factors associated with MetS (270–274). In this context, the use of

GI have also been explored as a dietary alternative to reduce the carbohydrate absorption rate, and hence to treat CVD. Two independent meta-analyses of 28 RCTs with a follow-up between 4 and 78 weeks have shown a beneficial effect of low-GI vs. high-GI on total cholesterol and LDL (275,276). However, these results were not supported by the data of another recent meta-analysis of 14 RCTs with a follow-up greater than 6 month where no effect was found between interventions with different GI and blood lipids. However, the authors reported a beneficial effect of low-GI interventions in C-reactive protein (CRP) and insulin concentrations (277).

In this context, observational studies have associated high dietary GI with an increased risk of coronary heart disease and stroke. Four different meta-analyses of observational studies have assessed the link between GI on CVD risk and have found similar results (278–281). The most recent and more extensive of them found 26% increased risk of CHD in women, but not in men, allocated in the highest quartile of dietary GI in comparison with those in the lowest. Similar results were found when stroke was the main outcome, although in this case increased risk was associated in both men and women (278).

Several investigators have suggested that metabolic effects generated after the consumption of high GI food could be associated with an increased risk of several types of cancer (282–288). In particular, hyperinsulinemia have been pointed as the unifying mechanism for the developing of several types of cancer (289,290). Observational studies evaluating the associations of GI and cancer have found different results depending on the type of cancer. A recent meta-analysis evaluating diabetes-related cancers (bladder, breast, colon–rectum, endometrium, liver and pancreas) found a pooled RR (95 % CI) of diabetes-related cancers of 1.07 (1.04, 1.11) in a comparison of the highest and lowest categories of GI. In an specific analysis of cancer type, only increased risk of breast cancer (RR 1.06; 95 % CI 1.02, 1.11) and colorectal cancer (RR 1·08; 95 % CI 1·00, 1·17) was associated with higher dietary GI (291). Molholland et al. conducted a meta-analysis of 23 cohorts and case-control studies evaluating the associations of GI and risk of digestive tract neoplasms. Authors didn't find any significant association with GI and the different

cancer types, although authors stated that there were insufficient data for the majority of the types (287).

4.2 Glycemic load

As stated before, the concept of the GI is based exclusively on the type of carbohydrates compounding the food and a fixed amount of available carbohydrates, normally 50 g. The quantity restriction was established to provide a food ranking, however, this point can create some limitations of daily management in which different carbohydrates amounts are eaten during meals. Because this, Walter Willet and colleagues at Harvard defined the GL in 1997 as the arithmetic product of GI and carbohydrate amount (264).

Firstly, the physiological validity of the GL concept was questioned due to its mathematical conception and the lack of experimental studies evaluating its correlation with glycemic and insulinemic responses evoked by different foods. Trying to resolve this, Brand-Miller et al. conducted a feeding trial where glycemic and insulinemic responses were measured in healthy subjects after the consumption of 10 different foods. The results of this feeding trial demonstrated that calculated GL can predict both glycemia and insulinemia (292). However, the study has several limitations. First, the participants of the study were healthy lean subjects and the obtained results cannot be extrapolated to other populations with associated disease. Second, tested foods were only individual foods and the GL ability to predict glycemic and insulinemic responses to mixed meals was still unknown. To resolve this second question, the group of Professor Brand-Miller conducted a new study a few years after where several individual foods and mixed meals were evaluated (293). Again, the results indicated that GL have a better prediction of glycemic (92%) and insulinemic (77%) responses of individual foods than carbohydrate content. When mixed meals were tested, similar, but lower correlations were found between GL and glycemic (76%) and insulinemic (68%) responses.

Ultimately, the validity of GL has been demonstrated with the observational and intervention studies where this dietary factor has been associated with disease risk or has been used as dietary

tool for prevention or treatment. Several epidemiological studies have been conducted since the GL concept was created in 1997. Like GI, GL has been associated with chronic diseases like T2DM, obesity, MetS, CVD and cancer (260,262,294–296).

Due to the ability to predict glycemia, GL has been investigated as a dietary factor for the prevention of T2DM. Prospective cohort studies have investigated the associations of GL and risk of T2DM with inconsistence results (263,264,267,297–306). Some of them found weak or contradictory observations (300–306), whereas the others found strong associations (263,267,297–299). In a meta-analysis including all prospective studies published to date, the authors reported a strong and consistently lower risk of T2DM among those subjects consuming low-GL diets. A 100-g incremental in dietary GL was associated with a 45% (95% CI: 1.31, 1.61, p<0.001) increased risk of T2DM in 757984 men and women (294).

CVD have also been directly associated with GL. Epidemiological studies have found a positive association between GL and, CHD and stroke, especially in women (278,279,307). Ma et al., found a consistent associations between GL and CVD (HR highest vs lowest categories: 1.23; 95% CI: 1.11–1.36) in a meta-analysis including 229,213 participants and more than 11,363 cases. In a stratified analysis, authors found a stronger association among Caucasian women (307). This results were supported by a two recent meta-analyses with similar results (278,279), where stronger associations were found between GL and CHD, especially in women.

The scientific community has also investigated the associations between GL and cancer, findings were similar than those shown previously regarding GI (282–288). GL has also been associated with a 21% increased risk of endometrial cancer when higher categories of GL were compared with the lowest (287).

4.3 Epidemiological studies

As explained previously, GI and GL have been associated with several chronic conditions including T2DM, CVD and cancer. However, GI and GL have also been investigated for the prevention and treatment of obesity.

Several prospective cohort studies have investigated the link between dietary GI and GL with anthropometrical measurements and with an increased risk of obesity (308–319). The most investigated measurement is BMI. Several studies have linked both GI and GL with BMI, finding inconsistent results (309,313,314,317,319–321). Ma and co-workers were the first in assess the associations between the type of carbohydrates and BMI in 572 healthy American adults. BMI was found to be positively associated with GI, but not with GL (320). Similar results were found in a cohort of 3931 Japanese young adults. Murakami et al found a positive association not only with GI and BMI (lowest vs. highest quintiles: 20.8 and 21.2 kg/m^2, p for trend =0.03), but also with GL (lowest vs. highest quintiles: 20.5 and 21.5 kg/m^2, p for trend =0.0005) (319). However, other investigators have found inverse (309,313,314) or no (311,317) association between BMI and GI or GL. Two studies conducted in Mediterranean population (Spain and Italy) found inverse associations between GI/GL and BMI. Mendez and coworkers were the first in report this inverse association in 8,195 Spanish adults. After adjusting for total energy intake, mean difference in BMI between the highest and lowest GL tertile was -0.71 kg/m^2 ($p<0.05$) for women. No significant association was found in men. In a similar analysis, Rossi et al also found an inverse association between GL, and also GI, and BMI. Compared with the lowest tertile, the coefficient for the third tertile of GI were -0.46 (-0.74, -0.19) among men and -0.81 (-1.13, -0.49) among women. Coefficients for GL were -0.79 (-1.14, -0.45) among men and -1.33 (-1.73, -0.94). The same authors also analyzed the correlation between GI and GL, and waist-to-hip ratio without significant results (313). GL has also been associated with obesity prevalence in 1078 Korean men and women. Those participants in the highest tertile of GL had a 50% less chance to be obese compared with those in the lowest (314).

The different types of carbohydrates have also been associated with waist circumference. Four different studies have evaluated this association with inconsistent results (310–312,317). Two of

the four studies found a positive significant association between GI and waist circumference and the other two not (310,317). In a cohort of 89432 participants, aged 20-78 years from five European countries, Du and collaborators observed that whit every 10-point higher in GI, waist circumference increased by 0.19 cm per year (95% CI: 0.11, 0.27) (311). GI has also been associated with a large weight girth in a cohort with 10912 participants from the Cooper Center Longitudinal Study. In this study, men and women allocated in the highest quintile of energy-adjusted GI were associated with a 27% (95% CI: 1.07, 1.51) and 74% (95% CI: 1.04, 2.89) more risk of large waist girth prevalence than those allocated in the lowest, respectively. However, GL was associated with inversely with large waist girth (OR: 0.52; 95% CI: 0.43, 0.63) in men, but not in women.

4.4. Clinical trials

The usefulness of the GI concept to reduce body weight has been investigated in a large number of diverse trails with different length, approximations and populations. The few systematic reviews and meta-analysis published to date have found a modest beneficial effect of low-GI diets in comparison with high-GI diets or low-fat diets, although there is a significant amount of inconsistency in the current findings (260,322). The majority of clinical trials conducted to assess the effect of GI/GL on weight loss used a parallel design and compared low-GI/GL diets in comparison to either low-fat or high-GI/GL diets.

To our knowledge, from the 26 identified clinical trials, 6 have found a significant beneficial effect of GI or GL on weight loss (323–328). One of them is the study conducted by Abete and collaborators where 32 participants, 14 females and 18 males, were randomized either to an energy-restricted low-GI diet or high-GI diet during 8 weeks. At the end of follow-up, participants allocated in the low-GI diet had a significant greater reduction in body weight than the high-GI group (−7.5 ± 2.9% vs −5.3 ± 2.6%; p = 0.032, respectively). The rest of clinical trials conducted to date couldn't achieve significant differences between intervention groups although the majority of them found a beneficial trend in Low-GI/GL interventions (329–340). Only the study

of Bellisle et al. found greater body weight reductions in control group, a Weight Watchers POINTS programme for 12 weeks, than the low-GI,high-carbohydrates group.

Three more trails have evaluated the effects of GI on weight loss with a different approximation. All three studies were clinical trial with multiple interventions combining GI with other weight-loss strategies. However, none of them found significant differences between interventions (341–343).

4.5 Potential mechanisms

Several physiological mechanisms have been proposed to link dietary GI and body weight or obesity. The most accepted are substrate oxidation, satiety and inflammation and they could be based on the postprandial metabolic environment precipitated by hyperglycaemia and hyperinsulinemia, which accelerate glucose oxidation and stimulate fat storage.

4.5.1 Substrate Oxidation

Due to postprandial insulin modulation by GI foods, some investigators have assessed the effect of GI on fuel partitioning and obesity (344,345). Short-, medium- and long-term studies failed to demonstrate that meals or diets differing in GI have significant effects on carbohydrate and fat oxidation and body composition. Ritz et al. evaluated fuel oxidation after the ingestion of 50 g of carbohydrates from glucose and manioc starch in non-obese healthy subjects for 6 h using a crossover design. Cumulative fat oxidation was not different between carbohydrate loads. Díaz et al. evaluated the effect of high- and low-glycaemic breakfast and lunch on fuel oxidation in obese women using a crossover design. Similarly, no differences between postprandial non-protein respiratory quotient after breakfast and lunch were observed. Some authors have state that probably differences in insulin concentrations between low-GI and high-GI diets are not sufficient to modify fuel oxidation.

4.5.2 Satiety

Satiety modulation also appears to be a potential mechanism relating low-GI and weight loss. High insulin and low glucagon responses generated after the ingestion of high-GI meal enhances glucose uptake in the muscle, liver and fat tissue. Moreover, lipolysis is inhibited and hepatic glucose production is limited. This specific metabolic environment, where carbohydrate and fat are inhibited in the postprandial state, may lead a quicker hunger responses and lower satiety (344).

Short-term satiety has been shown to increase in the vast majority of studies, although results have been inconsistent in long-term studies (346–348). Acute clinical trials have evaluated the effect of different GI foods or meals at postprandial period with significant results. Arumugan et al., conducted an acute clinical trial where they examined the effects of variations in postprandial glycemia and insulinemia on subjective satiety in 14 overweight and obese women. After 4 hours, participants consuming high-GI beverages indicated significantly higher ratings of hunger and prospective intake than those in the low-GI group (349). Similarly, Reynolds and coauthors assess the effect of either low or high glycemic meals during all day-long (10 h) on blood concentrations of glucose, insulin, cholecystokinin and ghrelin in 12 healthy lean subjects. Cholecystokinin concentrations were higher during the initial 7 hours (nearly 60% higer in low-GI group than high-GI group, P=0.046), but this effect was not observed at 10 hours (350).

Short/mid-term clinical trials (1-12 weeks) have failed to found significant differences in satiety ratings between interventions with different GI (337,351–354). In the study of Alfenas and collaborators, 39 healthy adults consumed only low- or only high-GI foods *ad libitum* in the laboratory for 8 days. Glucose and insulin concentrations as well as appetitive sensations were determined before and for 2 h following breakfast and lunch on days 1 and 8. There were no significant differences in plasma glucose or insulin responses, appetitive ratings, or food intake between treatments (352).

4.5.3 Inflammation

Chronic or low-grade inflammation is now considered a key factor in the development of several chronic diseases, including T2DM (355) and CVD (356). Also, inflammation rise as an alternative mechanism underlying the beneficial effects of low-GI foods on obesity control and its metabolic derangements.

Associations between GI/GL and inflammatory markers have been investigated in observational studies (301,357–363). The majority of the studies have evaluated the associations of dietary GI or GL and hsCRP. Six of the eight studies reported associations confined to either GI or GL were related to increased hsCRP (301,357,358,360,361,363). Only the studies of Huffman (362) and Murakami (359) found no associations between dietary GI or GL and hsCRP.

Some intervention trails have also evaluated the effect of GI on inflammatory markers, specially hsCRP (364–376). Three GI/GL intervention studies reported that reductions in hsCRP (372,375) -or IL-6 (369) -in the low-GI/GL group were significantly larger than changes in the control group. In 4 more studies, although no significant effects were found between intervention groups, a beneficial trend was observed (364,367,368,374). The rest of the mentioned studies did not found significantly greater reductions in hsCRP or IL-6 concentrations in the low-GI/GL group (365,366,370,371,373,376).

II. JUSTIFICATION

Overweight and obesity are described as one of the major health problems worldwide by the WHO. In 2008, it was estimated that more than 1.4 million adults aged between 20 and older were overweight and approximately 500 million were obese.

The main reasons for the enormous increase in overweight and obesity are physical inactivity and loss of healthy dietary habits. Thus, lifestyle interventions are the principal tool for the prevention and treatment of overweight and obesity and its associated comorbidities.

Traditionally, low-fat energy-reduced diets have been recommended for the majority of the scientific and medical associations to prevent or treat obesity and its associated CVD risk factors. However, nowadays, the potential beneficial role of the dietary carbohydrates, especially the quality of those, has been putted into consideration as a valid alternative for the prevention and treatment of obesity. The GI concept, introduced in the eighties by Professor Jenkins and coworkers, has been postulated as a dietary tool for the management of several chronic diseases such as T2DM, CVD, obesity, MetS and cancer. Although strong scientific evidence have been published regarding the beneficial effect of GI, and also GL, on the management of T2DM, inconsistent results have been shown with other chronic conditions, including obesity and MetS.

Few observational studies have evaluated the cross-sectional associations between GI/GL and MetS and its features with inconsistence results. Moreover, the association between GI/GL and the incidence of new cases of MetS has never been investigated before. Due to the actual inconsistency and the lack of knowledge in the available scientific evidence in the matter of GI/GL and MetS, we decided to evaluate this matter in the framework of the PREDIMED study, a cohort of individuals at high CVD risk.

A low chronic inflammatory status has been pointed out as a key factor involved in the pathophysiology of several metabolic diseases. The inflammatory trigger in obesity could be due an excess of nutrients. Some investigators have suggested inflammation as one of the possible mechanisms linking GI and obesity and its associated comorbidities. In this sense, several observational studies have assessed the link between GI and inflammation, although most of them have only focused on CRP and were not controlled by potential confounders as fiber.

The scarcity and the inconsistency of the evidence available on the effect of dietary GI and GL on adipokines led us to examine the changes in dietary GI and GL and changes in several adipokines and related metabolic risk markers of obesity and diabetes in a cohort of elderly subjects at high cardiovascular risk.

Finally, due to the limited evidence obtained from prospective observational studies, we have aimed to investigate the potential beneficial effects of GI on obesity and its comorbidities in the context of a randomized controlled trial. Owing to that we have designed the GLYNDIET study to assess the efficacy of two moderate-CH diets and a low-fat diet with different GIs on weight loss and the modulation of satiety, inflammation and other metabolic risk markers.

III. HYPOTHESIS

A greater dietary GI and/or GL are associated with an increased risk of MetS development or any of its features in a cohort of participants at high cardiovascular risk.

A greater dietary GI and/or GL are associated with higher concentrations of peripheral adipokines and inflammatory markers in a cohort of participants at high cardiovascular disease risk.

A chronic consumption of low-GI/ low-GL energy restricted diet may be more effective than isocaloric high-GI or low-fat diets at reducing body weight and improving metabolic profile, through an increased satiety and a beneficial inflammatory modulation.

IV. OBJECTIVES

To analyze the association between dietary GI and GL and the risk of to develop MetS and its features in a high cardiovascular risk population.

To analyze the relationship between dietary GI and GL, peripheral adipokines and inflammatory markers in a high cardiovascular risk population

To analyze the effectiveness of a high GI/GL diet versus a low-GI/GL and a low-fat diet in body weight loss and the improvement of metabolic profile, through the modulation of some mechanisms related to satiety, inflammation and other metabolic risk markers.

V. METHODS

The PREDIMED Study

The PREDIMED study (Prevención con Dieta Mediterránea) is a large, parallel group, multicenter, controlled, randomized clinical trial, aiming to assess the effect of Mediterranean Diet on the primary prevention of CVD (myocardial infarction, stroke, and death from cardiovascular causes) in elderly subjects at high cardiovascular risk. Secondary end points were death by any cause, heart failure with pulmonary edema, new-onset diabetes mellitus, dementia, and cancer incidence other than non-melanoma skin cancer. Additionally, other intermediate variables such as body weight, blood lipids, blood pressure, fasting glucose and markers of inflammation were also evaluated. (www.predimed.org)

Study Population

Participants were community-dwelling men and women, aged 55–80 and 60–80 years, respectively, with no CVD at enrolment and who fulfill the inclusion criteria. The inclusion criteria were:

a. Type-2 diabetes. Diagnosis of type-2 diabetes is based on at least one of the following criteria:
   - Current treatment with insulin or oral hypoglycemic drugs.
   - Fasting glucose > 126 mg/dl (fasting is defined as no caloric intake at least for 8 hours).
   - Casual glucose > 200 mg/dl with polyuria, polydipsia, or unexplained weight loss.
   - Glucose > 200 mg/dl in two measurements after an oral glucose tolerance test

OR

b. Three or more of the following risk factors:
   - current smoker (>1 cig/day during the last month)

- HBP (systolic BP>=140 or diastolic BP>=90 mmHg or under antihypertensive medication)
- LDL-cholesterol >= 160 mg/dl
- HDL-cholesterol <= 40 mg/dl independently of lipid-lowering therapy
- body mass index >=25 kg/m2
- family history of premature CHD (definite myocardial infarction or sudden death before 55 years in father or male 1st-degree relative, or before 65 years in mother or female 1st-degree relative)
- If the HDL-cholesterol level is >=60 mg/dL, one risk factor should be subtracted.

Major exclusion criteria are:

a. Documented history of previous CVD, including CHD (angina, myocardial infarction, coronary revascularization procedures or existence of abnormal Q waves in the electrocardiogram (EKG)), stroke (either ischemic or hemorrhagic, including transient ischemic attacks), and clinical peripheral artery disease with symptoms of intermittent claudication.
b. Severe medical condition that may impair the ability of the person to participate in a nutrition intervention study (e.g. digestive disease with fat intolerance, advanced malignancy, or major neurological, psychiatric or endocrine disease).
c. Any other medical condition thought to limit survival to less than 1 year.
d. Immunodeficiency or HIV-positive status.
e. Illegal drug use or chronic alcoholism or total daily alcohol intake >80 g/d.
f. Body mass index > 40 kg/m2.
g. Difficulties or major inconvenience to change dietary habits.
h. Impossibility to follow a Mediterranean-type diet, for religious reasons or due to the presence of disorders of chewing or swallowing (e.g., difficulties to consume nuts)
i. A low predicted likelihood to change dietary habits according to the Prochaska and DiClemente stages of change model (377).

j. History of food allergy with hypersensitivity to any of the components of olive oil or nuts.
k. Participation in any drug trial or use of any investigational drug within the last year.
l. Institutionalized patients for chronic care, those who lack autonomy, are unable to walk, lack a stable address, or are unable to attend visits in the PCC every 3 months.
m. Illiteracy.
n. Patients with an acute infection or inflammation (e.g., pneumonia) are allowed to participate in the study 3 months after the resolution of their condition.

Subjects were recruited from October 2003 to June 2009 in the different recruitment centers all around Spain (Málaga, Sevilla, Balearic Island, Barcelona, Reus-Tarragona, Pamplona, Basque Country, Valencia, Gran Canaria).

Intervention

The participants included in the study were randomly assigned in a 1:1:1 ratio to one of three nutritional education interventions: a Mediterranean diet supplemented with extra-virgin olive oil (approximately 1 litre per week), a Mediterranean diet supplemented with 30g of mixed nuts (15g of walnuts, 7.5 g of hazelnuts and 7.5 of almonds), or a control group in which participants received counselling to follow a low-fat diet according to the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (378). The dietary intervention was conducted by registered dietitians who advised and encouraged the study participants to follow the assigned intervention diet. After two screening visits, participants who were randomized in one of the three intervention diets had an individual baseline visit and a group session. Every three month, group sessions were scheduled separately for every intervention diet where participants were provided with written material including shopping lists, weekly meal plans and cooking recipes, and supplemental foods at no cost for those participants allocated to the Mediterranean diets. Olive oil and nut industry companies are committed to supplying for free the food supplements used in the study. Yearly, general medical questionnaire (**Appendix 1**), including cardiovascular risk factors; past medical history; pharmacological treatment; family

history of ischemic cardiopathy, hypertension and diabetes; tobacco use; alcohol intake and socioeconomic status, and food frequency questionnaire (FFQ) (**Appendix 2**) were obtained.

Dietary assessment

At baseline and annually thereafter, a validated 137-item FFQ was administrated to estimate average daily nutrient intake over the previous 12-month period (379). The FFQ was designed to be semi-quantitative and the frequencies of consumption of the food items were reported on an incremental scale with nine levels (never or almost never, 1–3 times per month, once per week, 2–4 times per week, 5–6 times per week, once per d, 2–3 times per d, 4–6 times per d and more than six times per d). Energy and nutrient intake was calculated from Spanish food composition tables (380,381).

With glucose as a reference scale, GI values for each food were extracted from the international GI and GL values (382). The average daily dietary GI was calculated by multiplying the GI of individual foods by the percentage of total energy contributed by carbohydrate (∑[GI food item × (g carbohydrate per serving food item × servings consumed per day/g carbohydrate consumed per day)]). Dietary GL was calculated by multiplying the daily GI of each food by the amount of carbohydrate consumed and dividing the product by 100((daily GI × g carbohydrate consumed per day)/100), and then adding up the values for all foods (257,383). The FFQ was validated for dietary GI and GL. Reproducibility and relative validity for dietary GI explored by the intraclass correlation coefficient was 0.321 and 0.244, respectively, and 0.846 and 0.525 for dietary GL.

A yearly 14-item questionnaire was the primary measure used in this study to appraise adherence of participants to the Mediterranean diet (**Appendix 3**). Mediterranean Diet Adherence questionnaire was adapted from a previous questionnaire from a Spanish case-control study for myocardial infraction (384). In addition to the 9 initial items from the original questionnaire (385), 5 extra items were added to assess adherence to the traditional Mediterranean diet foods and cooking habits.

Anthropometric and biochemical measurements

Anthropometric measurements and blood pressure were measured at baseline and every year during the follow-up. Body weight and height were measured wearing light clothing and no shoes by trained personal with calibrated scales and wall-mounted stadiometer, respectively. Waist circumference was measured with an anthropometric tape midway between the lower rib and the superior border of the iliac crest. Blood pressure was measured in triplicate with a 5-min interval between each measurement with a validated semiautomatic oscillometer (Omron HEM-705CP, Hoofddorp, Netherlands).

Leisure-time physical activity was evaluated using the validated Spanish version of the Minnesota leisure-time physical activity questionnaire (386) (**Appendix 4**).

At baseline and yearly, blood samples were obtained in fasting conditions and aliquots were kept frozen (-80ºC) in a Biobank. Plasma glucose, serum cholesterol, HLD cholesterol, and triglycerides concentrations were determined using standard enzymatic automated methods. In patients whose triglycerides were less than 400 mg/dl, LDL-cholesterol concentrations were estimated using Friedewald formula (387).

Peripheral adipokines and inflammatory markers were determined in 511 consecutively admitted participants recruited from the PREDIMED trial centers in Reus and Barcelona. Plasma adiponectin, adipsin, ghrelin, glucagon-like peptide 1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), IL-6, leptine, plasminogen activatior inhibitor-1 (PAI-1), resistin, TNF-α and visfatin were determined using the Bio-Plex cytokine assay (Bio-Rad Laboratories Inc., Hercules, CA, USA) according to manufacturer's instructions.

Metabolic Syndrome definition

Prevalent MetS and its features were defined in accordance with the updated harmonized International Diabetes Federation and the American Heart Association/National Heart, Lung, and Blood Institute criteria (152). Participants were considered to have MetS if they had three or

more of the following components: a) abdominal obesity for European individuals (≥88 cm and ≥102cm in women and men, respectively), b) hypertriglyceridemia [≥150 g/dL] or drug treatment for elevated TG, c) low concentrations of HDL-cholesterol [<40 mg/dL in men; <50 mg/dL in women] or drug treatment for low HDL-cholesterol, d) high blood pressure (systolic ≥130 and/or diastolic ≥85 mmHg) or antihypertensive drug treatment, e) high fasting glucose [≥100 mg/dL] or drug treatment for diabetes.

The GLYNDIET study.

The GLYNDIET study has been designed as a 6-month randomized, parallel, controlled clinical trial aiming to evaluate the effect of the dietary GI on weight loss, satiety, glucose and insulin metabolism, lipid profile, inflammation and other emergent metabolic risk markers.

Study Population

Eligible participants were community-dwelling men and women aged between 30 and 60 years, with a BMI between 27 and 35 Kg/m2.

Participants were excluded if they had one of the following criteria:

a. Non-controlled T2DM defined as a HbA1c > 8%.
b. Systolic blood pressure (SBP) > 159 mmHg or diastolic blood pressure (DBP) > 99 mmHg.
c. Plasma LDL-cholesterol > 160 mg/dL.
d. Plasma triglyceride concentrations > 400 mg/dL.
e. Suspicion of secondary obesity
f. Presence of any inflammatory or chronic obst.ructive pulmonary disease, infection, active neoplastic, endocrine or haematological disease at the time of the study.
g. Blood leukocyte count ≥ 11 x 106 cells.
h. Use of anti-inflammatory drugs, steroids, hormones or antibiotics that could affect the parameters analysed in the study.
i. Changes in medication for lipid profile, diabetes or hypertension in the previous three months.
j. Active alcoholism or drug dependence, excluding tobacco use.
k. Restrictive diet 3 months before the study or weight loss > 5 kg in the previous 3 months.
l. Any medical condition that advised against being included in the study.
m. Problems in understanding the study or anticipated difficulty in making dietary changes according to the Prochaska and DiClemente model (377).

Subjects were recruited from the outpatient clinics in obesity of the University Hospital of *Sant Joan de Reus* and announcements made in the Reus (Spain) primary care centres of the *Institut Català de la Salut*.

Intervention

Participants fulfilling the inclusion criteria were randomly assigned to three different dietary intervention groups of the same size. Randomization was done by a computer-generated random-number sequence. Subjects were assigned to blocks of 3 participants balanced for sex, age (<45 and ≥ 45 years) and anti-diabetic medication use (yes or no). Subjects were advising on a: a low-GI diet (40% of energy from fat, 42% from low-GI carbohydrates and 18% from protein), a high-GI diet (40% of energy from fat, 42% from high-GI carbohydrates and 18% from protein) or a low-fat diet (30% of energy from fat, 52% from high-GI carbohydrates and 18% from protein). Recommended diets were isocaloric, and the amount of dietary fibre, do not differ between the three intervention groups. Diets were designed at 1500, 1700, 2000 and 2500 kcal/d, and all participants were categorized as having one of the four levels of dietary energy content after subtracting 500 kcal/d of the total estimated energy intake to achieve a desired weight loss.

Anthropometric and biochemical measurements

Clinical visits were scheduled at baseline, 15 days into the intervention, and then monthly until the end of the study. Body weight and height were measured using calibrated scales and a wall-mounted stadiometer, with subjects wearing light clothes and no shoes. Waist circumference was measured twice midway between the lowest rib and the iliac crest. Body composition was measured by bio-electrical impedance analysis (TANITA TBF-300, Arlington Heights, USA). Blood pressure was measured in the non-dominant arm, using a validated semiautomatic oscillometer (Omron HEM-705CP, Hoofddorp, Netherlands) in duplicate with a five-minute interval between each measurement. Physical activity was evaluated using the validated Spanish version of the Minnesota Leisure Time Physical Activity Questionnaire (24). Blood samples were collected at baseline and at the end of the study and were kept frozen (-80ºC) in a Biobank. Routine biochemical measurements were determined using standard enzymatic automated methods

(COBAS, Roche Diagnostics Limited, Basel, Switzerland). Specific biochemical measurements were determined in plasma using enzyme-linked immunosorbent assay commercial kits and MILLIPLEX® MAP Plex Kit (Merck Millipore, Billerica, USA). Insulin resistance and insulin secretion were estimated by the HOMA-IR and HOMA-BCF methods (388).

Dietary assessment

Dietary intake was estimated at baseline and in the 1st, 3rd and 6th months of intervention by means of 3-day dietary records including two workdays and a weekend day. Energy and nutrient intake were calculated using Spanish food composition tables (389).

Visual analogue scales (VASs)

At baseline, a fixed breakfast test, according to the nutritional characteristics of the intervention assigned diets, was served to all subjects. VASs were evaluated in a fasted state (immediately before the breakfast) and every thirty minutes after for a period of 2 hours in a controlled environment.

Full details of the GLYNDIET study protocol are detailed in the publication nº1.

VI. STUDY POPULATION

Study 1. Dietary glycemic index/load and peripheral adipokines and inflammatory markers in elderly subjects at high cardiovascular risk.

Subjects in the analysis were 511 consecutively admitted participants recruited from the PREDIMED trial centers in Reus and Barcelona.

Study 2. Effect of the glycemic index of the diet on weight loss, modulation of satiety, inflammation and other metabolic risk factors: a randomized controlled trial.

For the present study, all participants of the GLYNDIET study, recruited between February 2010 and May 2012, were analyzed.

Study 3. Dietary glycemic index and glycemic load are positively associated with risk of developing metabolic syndrome.

The total sample considered for the cross-sectional analysis was 6,622 participants, whereas for the longitudinal assessment contained only those subjects free of MetS at baseline (n=1832).

VII. PUBLICATIONS

Publication 1.

Title: Design and methods of the GLYNDIET study; assessing the role of glycemic index on weight loss and metabolic risk markers.

Authors: Martí Juanola-Falgarona, Núria Ibarrola-Jurado, Jordi Salas-Salvadó, Antoni Rabassa-Soler, Mònica Bulló.

Year: 2013
Journal: Nutrición Hospitalaria
Volume: 28
Pages: 382-390

Abstract:

BACKGROUND: GI and/or GL have been explored as an alternative for the prevention and/or management of obesity, cardiovascular disease, type 2 diabetes mellitus, and cancer. Objective: The purpose of the manuscript is to describe the design and methods used in the GLYNDIET Project, a study designed to simultaneously address the questions related to the exactly role of low glycaemic index carbohydrates has on weight loss.

METHODS: This study was designed as a 6-months randomized, parallel, controlled clinical trial aiming to evaluate the effect of the dietary GI on weightloss, satiety, glucose and insulin metabolism, lipid profile, inflammation and other emergent metabolic risk markers. Eligible subjects were community-dwelling men and women aged between 30 and 60 years, with a BMI between 27 and 35 kg/m2. Subjects were randomly assigned to three different dietary intervention groups (low-GI diet, high-GI diet or low-fat diet), that were isocaloric, and did not

differ in the amount of dietary fibre. Monthly, study subjects were scheduled for control visits where anthropometry, blood pressure, dietary habits, satiety and physical activity were assessed. Blood, urine and subcutaneous adipose tissue samples were collected at baseline and at the end of the study to further molecular and biochemical measurements.

DISCUSSION: The GLYNDIET study was designed to determine if there is a greater effectiveness of a carbohydrate restricted diet with low-GI compared to an isocaloric diet with carbohydrates of high-GI or low-fat diet on weight loss in middle long-term.

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Original

Design and methods of the GLYNDIET study; assessing the role of glycemic index on weight loss and metabolic risk markers

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Abstract

Background: **Glycemic index and/or glycemic load have been explored as an alternative for the prevention and/or management of obesity, cardiovascular disease, type 2 diabetes mellitus, and cancer.**

Objective: **The purpose of the manuscript is to describe the design and methods used in the GLYNDIET Project, a study designed to simultaneously address the questions related to the exactly role of low glycaemic index carbohydrates has on weight loss.**

Methods: **This study was designed as a 6-months randomized, parallel, controlled clinical trial aiming to evaluate the effect of the dietary glycemic index on weight-loss, satiety, glucose and insulin metabolism, lipid profile, inflammation and other emergent metabolic risk markers. Eligible subjects were community-dwelling men and women aged between 30 and 60 years, with a body mass index between 27 and 35 kg/m^2. Subjects were randomly assigned to three different dietary intervention groups (low glycemic index diet, high glycemic index diet or low-fat diet), that were isocaloric, and did not differ in the amount of dietary fibre. Monthly, study subjects were scheduled for control visits where anthropometry, blood pressure, dietary habits, satiety and physical activity were assessed. Blood, urine and subcutaneous adipose tissue samples were collected at baseline and at the end of the study to further molecular and biochemical measurements.**

Discussion: **The GLYNDIET study was designed to determine if there is a greater effectiveness of a carbohydrate restricted diet with low glycemic index compared to an isocaloric diet with carbohydrates of high glycemic index or low-fat diet on weight loss in middle long-term.**

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Key words: *Glycemic index. Weight loss. Inflammation. Satiety.*

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DISEÑO Y MÉTODOS DEL ESTUDIO GLYNDIET; EVALUANDO EL PAPEL DEL ÍNDICE GLUCÉMICO SOBRE LA PÉRDIDA DE PESO CORPORAL Y MARCADORES DE RIESGO METABÓLICO

Resumen

Introducción: **El índice glucémico y la carga glucémica se han postulado como una alternativa para la prevención y/o el manejo de la obesidad, enfermedades cardiovasculares, diabetes mellitus tipo 2 y cáncer.**

Objetivo: **Describir el diseño y los métodos utilizados en el proyecto GLYNDIET, un estudio diseñado para evaluar el papel del índice glucémico sobre la pérdida de peso corporal, la saciedad, la inflamación y marcadores de riesgo metabólico.**

Métodos: **Ensayo clínico, en paralelo, controlado, aleatorizado y de 6 meses de duración realizado en hombres y mujeres de entre 30 y 60 años, con un índice de masa corporal de entre 27 y 35 kg/m^2. Los sujetos fueron asignados aleatoriamente a una de las 3 intervenciones (dieta con carbohidratos de bajo índice glucémico, dieta con carbohidratos de alto índice glucémico o dieta baja en grasa). Los sujetos fueron citados mensualmente para realizar visitas control en las que se recogían datos a antropométricos, de presión arterial, hábitos dietéticos, sensación de saciedad y grado de actividad física. Al inicio y al final del estudio se recogieron muestras sanguíneas, urinarias y de tejido adiposo subcutáneo mediante biopsia abdominal.**

Discusión: **El estudio GLYNDIET se diseñó con el objetico de determinar si el consumo de una dieta con carbohidratos de bajo índice glucémico muestra una mayor efectividad sobre la pérdida de peso corporal y la modulación de factores de riesgo metabólico en comparación a una dieta con carbohidratos de alto índice glucémico o una dieta baja en grasas.**

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Palabras clave: *Índice glucémico. Pérdida de peso. Inflamación. Saciedad.*

Background

Overweight and obesity are one of the major public health concerns because the prevalence and its rapidly increasing worldwide. Moreover, obesity has been associated with the incidence of multiple co-morbidities such as type-2 diabetes (T2DM), hypertension, cardiovascular disease and cancer.[1] The most reliable explanation of this situation is changes occurred in lifestyle (i.e. dietary habits) of modern industrialized societies.[2]

Traditionally, low-fat diets have been widely recommended for weight control. Nevertheless, the interest on the amount and quality of dietary carbohydrates has been of a growing interest. In a meta-analysis of randomized controlled trials encompassing a total of 447 subjects, evidence was found to support the use of low-carbohydrate diets for weight reduction in short to medium term (up to 6 months).[3] However, the results of longer-term trials in terms of body weight reduction and metabolic benefits are highly controversial.[4-6]

Despite of that, dietary carbohydrates provide the most frequently and important source of energy worldwide, reaching between 45 and 60% of total energy intake.[7] In 1998, FAO recommended to classify carbohydrates according to their glycemic effect.[8] Since then, the control of glycemic index (GI) and/or glycemic load (GL), have been explored as a dietary alternative for the prevention and/or management of obesity,[9] cardiovascular disease,[10] T2DM,[11] and cancer.[12] In the scientific community there is a growing consensus on the protective effect of low GI/GL diets on the risk of chronic conditions such as T2DM, coronary heart disease and some types of cancer.[13] However its effect on obesity and satiety are less conclusive[14] and recently, the European Foods Safety Agency has considered insufficient the evidences to make recommendations for or against the use of glycemic index on obesity treatment.[15]

The knowledge of the mechanisms underlying the potential beneficial role of carbohydrates according to their GI classification could be of great interest in terms to design effective therapeutically strategies on obesity and its comorbidities. GI has been involved in fuel partitioning, although the magnitude of this effects seems to be not sufficient to modify body composition.[16] Increasing satiety has also been proposed as a potential mechanisms induced by low-GI foods for the control of weight-gain. However, the effect on satiety was observed only in acute clinical trials,[17-20] whereas studies conducted in the short/mid-term (1-12 weeks) or in the long-term (12 months or more) do not found any effect of the GI or GL on satiety control.[14,21-24] Finally, inflammation rise as an alternative mechanism underlying the beneficial effects of low-GI foods on obesity control and its metabolic derangements.[25-27] Nonetheless, most of these studies have been conducted in a reduced number of subjects, are of shortly duration and without control of dietary potential confounders. For these reasons the exactly role of GI on inflammation is still a matter of debate.

The GLYNDIET Project was designed to simultaneously address the questions related to the exactly role of low glycaemic index carbohydrates has on weight loss, and its underlying molecular mechanisms.

Methods/design

Study design

The GLYNDIET study has been designed as a 6-months randomized, parallel, controlled clinical trial aiming to evaluate the effect of the dietary glycemic index on weight-loss, satiety, glucose and insulin metabolism, lipid profile, inflammation and other emergent metabolic risk markers (fig. 1). The second objective is to assess the acute postprandial effects of breakfasts differing in its GI foods on satiety, glucose and insulin metabolism, lipid profile and systemic inflammation response. Thirdly, in a subgroup of patients, we evaluate chronic effect of the dietary glycemic index/load on adipose tissue expression of several biomarkers of stress.

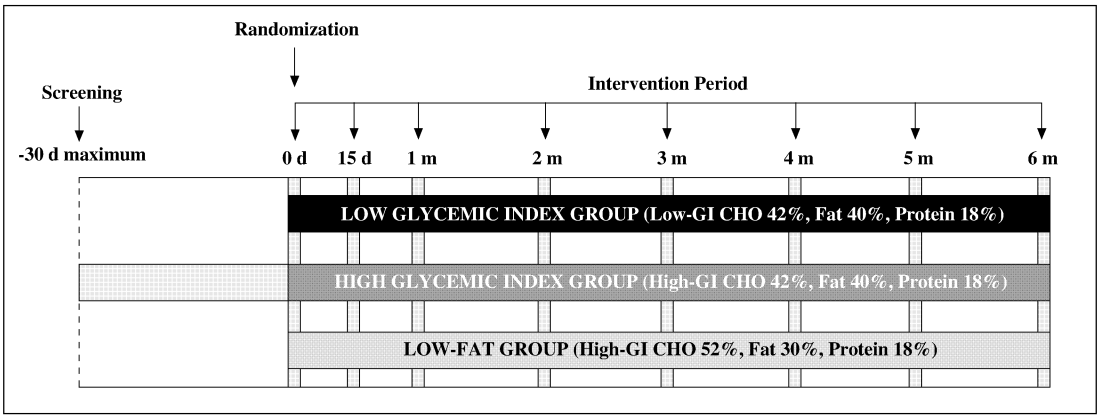

Fig. 1.—Study design. Intervention period and scheduled visits.

Eligibly subjects

Eligible subjects were community-dwelling men and women aged between 30 and 60 years , with a body mass index (BMI) between 27 and 35 kg/m^2. Subjects were excluded if they had one of the following criteria: a) non controlled T2DM defined as having a HbA1c > 8%; b) systolic blood pressure (SBP) > 159 mmHg or diastolic blood pressure (DBP) > 99 mmHg; c) plasma low-density lipoprotein (LDL) cholesterol > 160 mg/dL; d) plasma triacylglycerol (TAG) concentrations > 400 mg/dL; e) suspicion of secondary obesity; f) presence of any inflammatory or chronic obstructive pulmonary disease, infection, active neoplastic, endocrine or haematological disease at the time of the study; g) leukocyte count ≥ 11 x 10^6 cells; h) taking anti-inflammatory drugs , steroids, hormones or antibiotics that could affect the parameters analysed in the study; i) changes in medication for lipid profile, diabetes or hypertension in the three months previous of the study; j) active alcoholism or drug dependence, excluding tobacco use; k) having followed a highly restrictive diet for 3 months before the beginning of the study or latest weight loss (more than 5 kg in the last 3 months); l) medical condition that discourages the inclusion in the study; m) problems in to understand the study or anticipated difficulty in making dietary changes according to the Prochaska and DiClemente model.[28]

Recruitment

Subjects were recruited from the outpatient clinics in obesity of the University Hospital of *Sant Joan de Reus* and announcements made in the Reus (Spain) primary care centres of the *Institut Català de la Salut*.

Screening and enrolment procedures

Potential subjects contacted the research staff by telephone or during their clinical visits where they were asked for personal data, anthropometric measures and medical history. Eligible subjects interested in the study were scheduled in a screening face-to-face interview. During this screening interview, the objective and main details of the study were explained, and a signed informed consent was obtained from willing participants that potentially comply with inclusion criteria. Figure 2 shows the workflow of the study.

Interventions

Subjects fulfilling the inclusion criteria were randomly assigned to three equally sized different dietary intervention groups, by using a computer-generated random-number sequence. Subjects were assigned into blocks of 3 participants balanced by sex, age (< 45 years and ≥ 45 years) and anti-diabetic drugs use (yes or no). Subjects were advising on a:

a) Low-GI diet (40% of energy from fat, 42% from low-GI carbohydrates and 18% from protein).
b) High-GI diet (40% of energy from fat, 42% from high-GI carbohydrates and 18% from protein).
c) Low-fat diet (30% of energy from fat, 52% from high-GI carbohydrates and 18% from protein).

Recommended diets were isocaloric, and the amount of dietary fibre, do not differ between the three intervention groups.

Registered dieticians gave personalized advice to each participant with specific recommendations in each group related to the desired frequency of meals, the intake of specific foods with particular emphasis on the type of carbohydrate and cooking methods.

Subjects who were randomized to the low-GI diet were especially encouraged to eat whole grain cereals and pulses as the base of their diet, avoid the rice and potatoes, and were also recommended to select specific type of fruit (apple, orange, peach) and vegetables (courgette, tomato, onion) with low GI, avoiding the ripe pieces. They were advised to reduce the time cooking of carbohydrate rich-foods in order to maintain the low GI of the foods. The principal animal protein sources of the diet were white fish and white meat.

Contrary, participants randomized to the high-GI diet were encouraged to eat refined grain cereals, fruits (banana, kiwi, melon) and vegetables (carrot, green bean, cabbage) with high GI, and avoid pulses. Unlike the low-GI intervention, subjects on high-GI were advised to increase the time cooking in order to rise the GI of the foods. In this intervention group, intake of white fish and white meat were the main animal sources of protein.

Subjects randomized in low-fat diet were also advised to maintain a high-GI diet but with lower fat content. Additionally, daily sugar was substituted by glucose in order to rise GI of this intervention. In this case, they were recommended to avoid red meat and blue fish due its high fat content and also recommended to eat low-fat dairy products.

In order to facilitate the adherence to dietary interventions, we gave to the subjects a dossier containing a leaflet with written general dietary recommendations, biweekly menus (table I), and seasonal receipts. An informative website was available for all participants (http://www.glyndiet.org/). In order to obtain the desired weight loss, a 500 kcal restriction in diet was applied to each participant. Total daily energy expenditure for each participant was estimated using the WHO (2001) equations corrected by the physical activity degree.

Ethical committee

The Institutional Review Board of University Hospital of *Sant Joan de Reus* (Spain) approved the

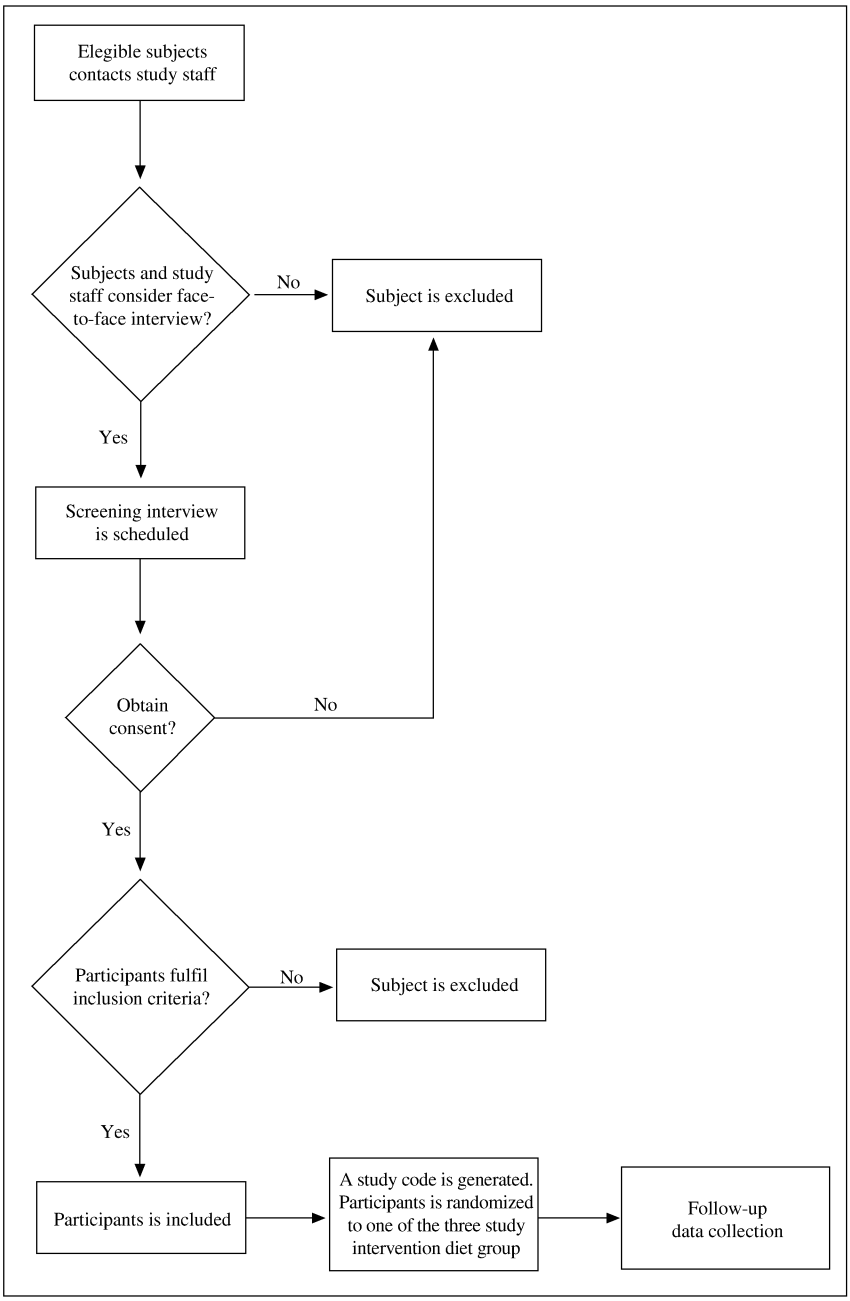

Fig. 2.—Workflow of the study.

study protocol on February 2009. The trial was registered in International Standard Randomized Controlled Trial Number Register (ISRCTN54971867).

Measurements

Individual examination visits were scheduled at baseline, after 15 days of intervention, and then monthly until the end of the study. Across the visits, different evaluations and questionnaires were conducted to assess changes on anthropometry and the adherence to the intervention.

Anthropometry and blood pressure

Each examination visit included the evaluation of anthropometry and blood pressure. Body weight and

Table I
Quantitative example of a daily menu for the three arms of dietary intervention

	Low-GI diet	*High-GI diet*	*Low-Fat diet*
Breakfast	Skimmed milk, whole-grain cereals or whole-grain bread with olive oil fruit and nuts	Skimmed milk, breakfast cereals with chocolate and fruit	Low-fat milk, white bread sandwich with white cheese and fruit
Mid-morning Snack	Whole-grain sandwich with white cheese and olive oil	White bread sandwich with ham and olive oil	Low-fat yogurt with glucose and white toast
Lunch	Stewed lentils with vegetables, baked sole with salad, fruit and whole-grain bread	Green salad, white pasta with Bolognese sauce, fruit and white bread	Mashed potato, grilled turkey with artichokes, fruit and white bread
Afternoon snack	Low-fat yogurt, fruit, whole-grain bread with olive oil	Full-fat yogurt, fruit and Rich Tea biscuits	Low-fat yogurt with breakfast cereals with chocolate, glucose, fruits
Dinner	Salad with goat cheese, omelette with vegetables, fruit and whole-grain bread	Rice salad, grilled salmon with vegetables, fruit and white bread	Vegetable soup, scrambled eggs with mushrooms, fruit and white bread

GI: Glycemic index.

height were measured using calibrated scales and a wall-mounted stadiometer with subjects wearing light clothes and no shoes by trained staff. Their body mass index was calculated as the weight (kg) divided by the square of the height (m). Waist circumference was measured twice at the midway between the lowest rib and the iliac crest. Body composition was measured by bio-electrical impedance analysis (TANITA TBF-300, Arlington Heights, USA). Blood pressure was measured in the non-dominant arm, using a validated semiautomatic oscillometer (Omron HEM-705CP, Hoofddorp, Netherlands), in duplicate with a five-minute interval between each measurement, and the mean of these values was recorded.

Dietary assessment

Dietary intake was estimated at baseline and at the 1st, 3th and 6th month of intervention by mean of 3-day dietary records including two workdays and a weekend day. Subjects were encouraged to weight the food that they eat; otherwise trained dieticians estimated weight using an illustrated book of food portions.[29] Energy and nutrient intake were calculated from Spanish food composition tables.[30] Values of GI for each food were extracted from the International Glycemic Index and Glycemic Load Values using glucose as the reference scale.[31] The dietary glycemic index was calculated according to the equation:

$$\text{Dietary GI} = \sum GI_a \times (CHO_a/CHO_{a\text{-}n})$$

where GI_a represents the glycemic index of the food, CHO_a the available carbohydrate of the food and $CHO_{a\text{-}n}$ represents the total available carbohydrate.

Dietary glycemic load was calculated as follow:

$$\text{Dietary GL} = \sum GI_a \times CHO_a/100$$

where GIa represents the glycemic index of the food, and CHOa the available carbohydrate of the food.

Satiety evaluation

Satiety was evaluated at baseline and at the end of the study. Participants completed a short subjective questionnaire measuring the rates of hunger, fullness, satiety and desire to eat at breakfast, lunch and dinner using visual analogue scales (VASs). VASs were represented by a 100 mm line that goes to 0 to 10, where 0 represents "extremely hungry" and 10 "I'm hungry as I've ever been".[32] Subjects had to rate their subjective levels of satiety before having each meal and every 30 minutes during four hours after.

Physical activity

As dietary intake, physical activity was evaluated 3 times along the intervention using the validated Spanish version of the Minnesota Leisure Time Physical Activity Questionnaire.[33] There was no specific intervention on physical activity during the 6 months of the intervention. Subjects were encouraged to continue with their normal patterns of physical activity.

Tolerance and side effects

In each month visit, dietitians assessed any adverse effects occurred by administering a checklist of symptoms including: mouth symptoms; bloating, fullness, or indigestion; altered bowel habit; and any other diet-related symptoms.

Biological samples collection and store

Blood and urine samples were collected at baseline and at the end of the study. Aliquots of EDTA plasma, citrate plasma, buffy coat and serum were kept frozen (-80º C) for further determinations of satiety markers, inflammatory cytokines and other metabolic risk markers. Specific RNA tubs were also collected and kept frozen at -20º C for further analysis of mRNA expression (Applied Biosystems, Life Technologies, UK). At the same time, platelets, erythrocytes and mononuclear cells were isolated from EDTA plasma tubes and preserved for further analysis. Simultaneously, complete blood cell count, fasting plasma glucose, glycosylated haemoglobin, lipid profile, urea and creatinine concentrations, transaminases and coagulation tests were determined in a centralized laboratory using routine analysis methods. The 24-hour urine samples were collected, the volume of the sample was quantified and aliquots of 2 ml were kept frozen at -80º C.

Additionally, adipose tissue samples were obtained in a subgroup of subjects at baseline and at the end of the study. Subcutaneous adipose tissue samples were removed by incisional biopsy on the right side of the abdomen under local anaesthesia The adipose tissue samples were immediately frozen in liquid nitrogen for a better preservation and were conserved at -80º C.

Evaluation of postprandial response

At baseline, a study test breakfast was served to all subjects according with dietary characteristics of the intervention group assigned. After 2 hours, a blood extraction was performed to collect blood samples for further biochemical analysis. Ratings of satiety were evaluated during a 4-h postprandial period using VASs.

Statistical analysis

Sample size was estimated considering the weight loss as the primary outcome. Based in previous studies,[34,35] sample size estimated was 33 subjects for Low-GI and High-GI groups and 25 subjects for low-fat group, with an alpha error of 5% and 90% of power. Expecting a 15% of dropouts, we decided to include 40 subjects for each one of the intervention groups to compensate the possible losses.

All analyses will be based on an intention-to-treat approach. Differences between the final and baseline visits for continuous measures will be expressed as means and standard deviation. Variables that did not fit a normal distribution (Kolmogorov-Smirnov test) will be treated in its logarithmic form. The primary analysis will be done by analysis of variance of repeated measures with change in BMI between final visit and baseline visit as the dependent variable and intervention group as the independent variable. We will also conduct post-hoc comparisons within groups to observe the individual effects of the interventions. In addition, we will assess the predictive capacity of inflammatory cytokines over the body weight loss through multiple linear regression models and the changes of these cytokines throw the 6 months are effected by the intervention after adjusting for potential confounders. Level of significance was set at $P < 0.05$. All analyses will be performed with the newest version of the statistical software package SPSS for windows.

Trial status

Enrolment was completed at the end of May 2012 with a total of 122 subjects. The intervention began in February 2010 and will end in November 2012.

A total of 543 persons were interested in the study. Of these, 289 individuals were eligible subjects, of whom 74 declined to participate, and 254 did not meet some of the study criteria. 215 eligible subjects were scheduled to the screening interview and 93 did not meet the inclusion criteria. Finally, 122 subjects were randomized to one of the three study interventions, 41 in the low-GI diet group, 41 in the high-GI diet group and 40 in the low-fat diet group (fig. 3). Baseline characteristics of the study subjects are shown in table II.

Discussion

Diet is the main modifiable factor for preventing and treating obesity and its associated comorbidities. It is therefore imperative to understand the exactly role of the different nutritional strategies on health, and to know what are the mechanisms that might explain such effects towards the design more effective therapeutic and preventive strategies. In opposition to the traditional dietary advices which postulated energy reduction mainly at the expense of fat for the obesity treatment, new nutritional strategies have been addresses not only through the change in the proportion of essential elements, but also the quality thereof. Over the past decade, a growing body of research has linked low GI/GL diets to weight loss. The majority of the studies found a trend in favor of low GI/GL diets, however there are several inconsistencies and no log-term studies, with large differences in dietary GI/GL interventions have been conducted. These discrepancies could be partially explained by the methodology of GI estimation of the diets through the International Glycemic Index and Glycemic Load Values.[31] The majority of these values are from studies conducted in Australia or North-America where the foods or their composition may differ from that consumed in the rest of the world. In our specific case, there are few Spanish products with GI values in the international tables. The estimation of the GI of the GLYNDIET interventions must be evaluated with caution.

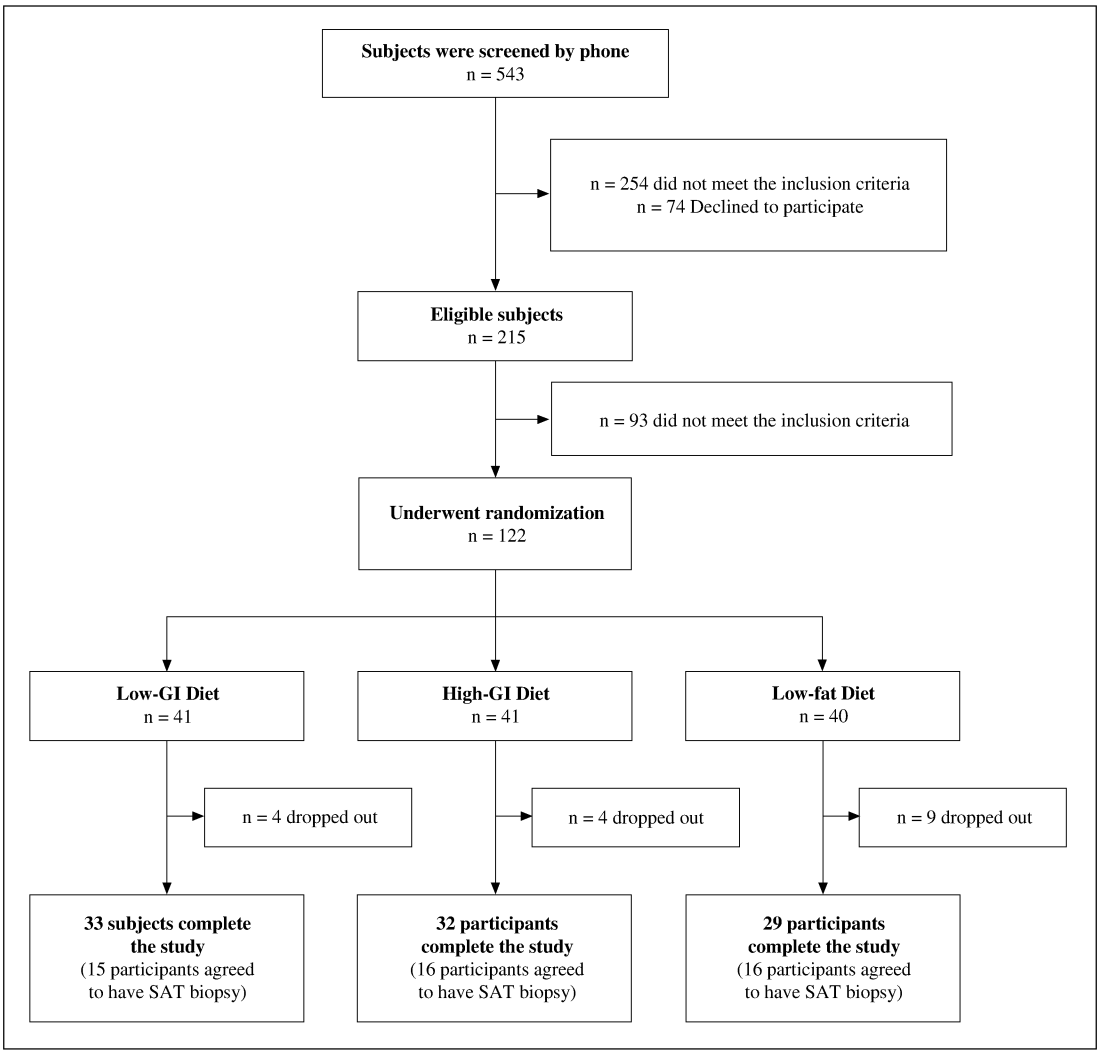

Fig. 3.—Flowchart of the study. SAT: Subcutaneous Adipose Tissue.

Table II
Baseline characteristics of study subjects by intervention group

	Low-GI (n = 41)	*High-GI (n = 41)*	*Low-Fat (n = 40)*	*p*
Men/Women (n)	8/33	7/34	9/31	0.828
Age (y)	43 ± 7	44 ± 8	44 ± 8	0.529
Weight (kg)	82.7 ± 9.6	82.8 ± 9.8	83.5 ± 10.6	0.913
BMI (kg/m^2)	31.2 ± 2.1	30.8 ± 2.2	30.8 ± 2.2	0.602
Waist circumference(cm)	101.8 ± 7.7	100.4 ± 8.7	103.1 ± 6.9	0.295
Systolic blood pressure (mmHg)	128.0 ± 17.1	128.5 ± 15.1	131.3 ± 13.9	0.592
Diastolic blood pressure (mmHg)	80.2 ± 10.8	81.2 ± 9.6	82.8 ± 9.1	0.489
Current Smoker n (%)	8 (20)	5 (12)	5 (13)	0.573

Data are given as mean (SD) or number (%) unless otherwise indicated. P values of the difference between intervention group (ANOVA for the continuous variables and a 2 test for categorical variables).

Conclusions

The GLYNDIET study has been designed to determine if there is a greater effectiveness of a carbohydrate restricted diet with low-GI compared to an isocaloric diet with carbohydrates high GI or low-fat diet on weight loss in middle long-term. This study will address the different molecular mechanisms that could explain the potential beneficial effect of low-GI carbohydrates on health from different perspectives: the control of satiety (visual analogue scales and biomarkers), modulation of systemic inflammation and the expression of markers of inflammation in adipose tissue, and modulation of the composition and/or activity of various cell populations (lymphocytes, erythrocytes, platelets) for their involvement in inflammatory processes of oxidation and coagulation . Therefore, the results obtained in this study will help establish new nutritional basis for the prevention and/or treatment of obesity and its comorbidities.

Competing interests

The authors declare that they have no competing interests.

Acknowledgments

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Publication 2.

Title: Dietary glycemic index/load and peripheral adipokines and inflammatory markers in elderly subjects at high cardiovascular risk.

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Abstract:

BACKGROUND AND AIMS: Epidemiological and clinical studies suggest that low-GI diets could protect against weight gain. However, the relationship between these diets and adipokines or inflammatory markers is unclear. In the present study we examine how the dietary GI and dietary GL are associated with several adipokines and related metabolic risk markers of obesity and diabetes in a cross-sectional and longitudinal manner.

METHODS AND RESULTS: 511 elderly community-dwelling men and women at high cardiovascular risk were recruited for the PREDIMED trial. Dietary data were collected at baseline and after 1 year of follow-up. The GI and GL were calculated. Plasma leptin, adiponectin and other metabolic risk markers were measured at baseline and after 1 year. At baseline, subjects in the highest quartiles of GI showed significantly higher levels of TNF and IL-6 than those in the lowest quartiles. Dietary GI index was negatively related to plasma leptin and adiponectin levels. After 1 year of follow-up, subjects with a higher increase in dietary GI or GL showed a greater reduction

in leptin and adiponectin plasma levels. There was no association between GI or GL and the other metabolic markers measured.

CONCLUSION: Our results suggest that the consumption of high-GI or high-GL diets may modulate plasma concentrations of leptin and adiponectin, both adipostatic molecules implicated in energy balance and cardiometabolic risk.

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Nutrition, Metabolism & Cardiovascular Diseases

Dietary glycemic index/load and peripheral adipokines and inflammatory markers in elderly subjects at high cardiovascular risk

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KEYWORDS
Glycemic index;
Glycemic load;
Inflammation;
Adipokines;
PREDIMED study

Abstract *Background and Aims:* Epidemiological and clinical studies suggest that low-glycemic index diets could protect against weight gain. However, the relationship between these diets and adipokines or inflammatory markers is unclear. In the present study we examine how the dietary glycemic index (GI) and dietary glycemic load (GL) are associated with several adipokines and related metabolic risk markers of obesity and diabetes in a cross-sectional and longitudinal manner.
Methods and Results: 511 elderly community-dwelling men and women at high cardiovascular risk were recruited for the PREDIMED trial. Dietary data were collected at baseline and after 1 year of follow-up. The GI and GL were calculated. Plasma leptin, adiponectin and other metabolic risk markers were measured at baseline and after 1 year. At baseline, subjects in the highest quartiles of GI showed significantly higher levels of TNF and IL-6 than those in the lowest quartiles. Dietary GI index was negatively related to plasma leptin and adiponectin levels. After 1 year of follow-up, subjects with a higher increase in dietary GI or GL showed a greater reduction in leptin and adiponectin plasma levels. There was no association between GI or GL and the other metabolic markers measured.

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Conclusion: Our results suggest that the consumption of high-GI or high-GL diets may modulate plasma concentrations of leptin and adiponectin, both adipostatic molecules implicated in energy balance and cardiometabolic risk.

Introduction

Chronic low-grade inflammation associated with increased adipocytokine production from adipose tissue is recognized as a central mechanism underlying obesity and its comorbidities. Two major adipocytokines, leptin and adiponectin, are involved in the regulation of energy balance and cardiovascular homeostasis. Leptin acts on the hypothalamus and regulates satiety, food intake and energy expenditure. Leptin also induces insulin resistance through its role in the phosphorylation of the insulin receptor [1]. Adiponectin increases fat oxidation, which reduces peripheral levels of fatty acids and increases insulin sensitivity [2]. The adiponectin/leptin ratio is suggested to be a useful parameter for assessing insulin resistance and atherogenic risk, and is even more sensitive and reliable than the homeostasis model assessment-insulin resistance (HOMAIR).

Since diet is the first line of intervention for preventing and treating obesity and cardiovascular risk factors, in the last years there has been growing interest in the role that different types of carbohydrates play in the modulation of postprandial glucose/insulin response, inflammatory markers and related molecules. The consumption of diets containing high amounts of whole grains and/or dietary fiber has been associated with low serum inflammatory markers. However, the many types of carbohydrates and fiber, have a different effect on postprandial glucose and insulin responses. In this regard, Jenkins introduced the concept of the glycemic index (GI), which ranks carbohydrate-rich foods in accordance with how much they raise blood glucose levels in comparison to standard foods [3]. The concept of glycemic load (GL) was subsequently developed to take into account the amount of food consumed [4]. Hypothetically, repeated postprandial hyperglycemia and hyperinsulinemia induced by foods with a high-glycemic index may cause insulin resistance, beta cell dysfunction and inflammation by many mechanisms. However, the results of epidemiological and interventional studies on this issue have been controversial. Although epidemiological studies have linked dietary GI and GL with obesity, type 2 diabetes and high risk of cardiovascular disease [5—8], they have not been able to consistently link them with inflammatory biomarkers [9—12]. Nevertheless, the few clinical trials that have evaluated the effect of dietary GI or GL on inflammation have reported an inconsistent reduction in circulating protein-C reactive levels and no effect on tumor necrosis factor (TNF) or interleukin-6 (IL-6) [13—15].

The scarcity and the inconsistency of the evidence available on the effect of dietary GI and GL on adipokines led us to examine the changes in dietary GI and GL and changes in several adipokines and related metabolic risk markers of obesity and diabetes in a cohort of elderly subjects at high cardiovascular risk.

Methods

Study population

We assessed 568 consecutively admitted participants recruited from the PREDIMED trial centers in Reus and Barcelona. The PREDIMED study is a large, parallel group, multicenter, controlled, randomized, 6-year clinical trial designed to evaluate the effects of the Mediterranean diet (MeDiet) on the primary prevention of cardiovascular disease. Candidates were community-dwelling men and women aged 55—80 years and 60—80 years, respectively, who had no previously documented cardiovascular disease and met at least one of the two following criteria: type 2 diabetes mellitus, or three or more cardiovascular risk factors [current smoking, hypertension (blood pressure $\geq$ 140/90 mmHg or treatment with antihypertensive drugs), low-density lipoprotein cholesterol level $\geq$ 160 mg/dL (or treatment with hypolipidemic drugs), high-density lipoprotein cholesterol level $\leq$ 40 mg/dL, BMI $\geq$ 25 kg/m^2, or family history of premature cardiovascular disease]. Exclusion criteria included any severe chronic illness, drug or alcohol addiction, history of allergy or intolerance to olive oil or nuts, or a low predicted likelihood of changing dietary habits according to the Proschaska and DiClemente stages-of-change model. Participants were randomly assigned to three interventions: MeDiet with virgin olive oil (VOO), MeDiet with mixed nuts and control group (low-fat diet). Both MeDiet groups received intensive education to follow the MeDiet and VOO or mixed nuts (walnuts, hazelnuts, almonds) were provided by the study. In the control group, participants were given advice to follow a low-fat diet. Full details of the study protocol have been published elsewhere [16]. The protocol was approved by the institutional review board of both Institutions and all participants provided written informed consent.

Dietary assessment

At baseline (before randomization) and after 1 year of follow-up participants were assessed by means of a 137-item FFQ to estimate average daily nutrient intake over the previous 12-month period. Detailed information regarding the development of FFQ and the reproducibility and validity of the questionnaire has been previously reported [17]. We estimated energy and nutrient intakes by multiplying the frequency of consumption of each food by the nutrient content estimated using Spanish food composition tables. The GI was determined using the Brand-Miller tables [18].

The average daily dietary GI was calculated by multiplying the GI of individual foods by the percentage of total energy contributed by carbohydrate ($\sum$[GI food item $\times$ (g carbohydrate per serving food item $\times$ servings consumed per day/g carbohydrate consumed per day)]) [19,20]. Dietary GL was calculated by multiplying the daily GI of each food by the amount of carbohydrate consumed and dividing the product by 100((daily GI $\times$ g carbohydrate consumed per day)/100), and then adding up the values for all foods.

Other measurements

All measurements were performed at baseline and after 1 year of follow-up using the same procedures. Information was collected on the subjects' medical history and use of medication. Leisure-time physical activity (LTPA) was evaluated using the validated Spanish version of the Minnesota LTPA Questionnaire. Height and weight were measured wearing light clothing and no shoes. Waist circumference was measured midway between the lowest rib and the iliac crest. Blood pressure was measured, using a validated semiautomatic oscillometer (Omron HEM-705CP, Hoofddorp, Netherlands). Fasting plasma glucose, serum cholesterol, HDL-c and triglyceride levels were measured using standard enzymatic automated methods in a centralized laboratory. In patients whose triglyceride levels were less than 400 mg/dL, LDL-c concentrations were estimated using the Friedewald formula. Plasma adiponectin, adipsin, ghrelin, glucagon-like peptide 1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), IL-6, leptin, plasminogen activator inhibitor-1 (PAI-1), resistin, TNF-α and visfatin were determined using the Bio-Plex cytokine assay (Bio-Rad Laboratories Inc., Hercules, CA, USA) according to manufacturer's instructions.

Statistical analysis

Subjects were categorized according to quartiles of dietary GI, GL or quartiles of changes in both cases. Chi-square tests and ANOVA were used to compare the qualitative traits and means of quantitative variables, respectively, across dietary GI quartiles. Inflammatory and metabolic risk markers were logarithmically transformed to achieve a normal distribution and the geometric mean and 95% confidence interval were used to describe these variables. Mean differences in inflammatory and metabolic risk markers were normally distributed. Analysis of covariance (ANCOVA), adjusted for potential confounding variables (sex, age, BMI, baseline waist circumference, baseline LTPA, smoking, insulin medication, presence of T2DM, w-3-fatty acids and fiber intake), was used to test for any differences in inflammatory and metabolic risk markers across GI or GL quartiles. Smoking and insulin medication were considered as a dichotomic variables (yes/no). Multiple logistic regression models were fitted to estimate the adjusted differences in the changes in inflammatory and metabolic risk markers between each of the three upper quartiles of GI or GL and the lower quartile at 1 year after adjusting for potential confounders (sex, age, LTPA, smoking, insulin medication, presence of T2DM, intervention group, and changes in BMI, waist circumference, and total w-3-fatty acid and fiber intake). The covariates selected were those that were clinically plausible and statistically significant correlated with more than one biochemical metabolic risk marker. Interaction tests for sex (product-terms, sex $\times$ glycemic index) and age (product-terms, age $\times$ glycemic index) showed that there were no statistically significant sex or age differences in the association between inflammatory markers and GI or GL quartiles. All statistical tests were two-tailed, and the significance level was $p < 0.05$. Statistical analysis was performed using SPSS 17.0.

Results

Of the 568 consecutively admitted participants recruited for the PREDIMED trial center in Reus and Barcelona with dietary data and blood samples at baseline and after 1 year of follow-up, 57 were excluded because of anti-inflammatory medication use at baseline, or showed leukocytosis (11.0×10^9/L). No under- and over-reporters of energy intake, considered as those whose energy intake was $\leq$800 or $\geq$4000 kcal/d in men and $\leq$500 or $\geq$3500 kcal/d in women were identified [21]. The general characteristics of the subjects are summarized in Table 1. Proportionally, more men were located in the highest quartile of GI than the reference quartile. The subjects in the highest quartile of GI showed a greater baseline waist circumference and higher total energy intake than those in lower quartiles. Moreover, an increasing linear trend was observed in total energy intake across GI quartiles. No significant differences were observed in baseline energy expenditure or LTPA between groups.

Tables 2 and 3, respectively, show the baseline inflammatory and metabolic risk markers levels in relation to the quartiles of dietary GI and GL, respectively. Significantly higher levels of TNF and IL-6 were observed in those subjects in the highest GI quartile. However, at baseline, no significant differences were observed in any inflammatory or metabolic risk markers analyzed in any of the quartiles of dietary GL. Plasma adiponectin levels decreased across both the GI and GL quartiles, although the differences did not reach statistical significance ($p = 0.114$, $p = 0.106$, respectively). The adiponectin/leptin ratio was lower as the GL quartile increased, although the difference did not reach the conventional level for statistical significance ($p = 0.059$).

In a longitudinal analysis, after 1 year of follow-up, no significant relationship was observed between changes in GI or GL and most of the metabolic risk markers measured (Tables 4 and 5, respectively). However, subjects in the highest quartile of changes in GI and GL showed a greater reduction in leptin and adiponectin plasma levels, even after adjusting for potential confounders. Additionally, those subjects in the highest quartile of changes in GL showed a significant increase in GIP ($p = 0.029$). A non-significantly higher decrease of BMI in those subjects allocated in the lowest quartile of change in GI (Q1: -0.49 ± 0.11, Q4: -0.11 ± 0.87, p for trend $= 0.071$) and a significantly higher decrease in the case of quartiles of change in GL (Q1: -0.49 ± 1.34, Q4: -0.36 ± 0.08, p for trend ± 0.021) were observed. In agreement with these data, a significant increase in total energy intake was

Table 1 Baseline characteristics of study subjects according to glycemic index quartiles.

	Q1	Q2	Q3	Q4	*p* for trend
	(*n* = 126)	(*n* = 129)	(*n* = 128)	(*n* = 128)	
Glycemic index	61.27 ± 0.39	69.02 ± 0.13	73.99 ± 0.13	80.09 ± 0.23	<0.001
Glycemic load	110.05 ± 1.74	149.92 ± 0.90	190.29 ± 1.23	263.79 ± 4.37	<0.001
Men/women (*n*)	43/83	55/74	54/74	75/53	<0.001
Age (y)	67.0 ± 0.5	67.2 ± 0.5	68.0 ± 0.5	66.4 ± 0.3	0.203
BMI (kg/m^2)	29.5 ± 0.3	29.2 ± 0.3	29.0 ± 0.2	29.2 ± 0.3	0.729
Waist circumference (cm)	99.4 ± 0.8	99.4 ± 0.8	99.2 ± 0.7	102.2 ± 0.8	0.029
Diabetic subjects (%)	60.3	58.1	56.2	45.3	0.076
Hypertensive subjects (%)	78.2	78.3	79.6	81.2	0.935
Dyslipidemic subjects (%)	69.0	77.5	71.1	75.8	0.382
Total energy intake (kcal/d)	2234 ± 48	2367 ± 47	2417 ± 45	2528 ± 50	<0.001
Carbohydrates (energy %)	39.61 ± 0.60	40.02 ± 0.49	41.91 ± 0.62	44.91 ± 0.59	<0.001
Fat (energy %)	40.14 ± 0.55	39.55 ± 0.45	38.74 ± 0.59	36.74 ± 0.51	<0.001
Protein (energy %)	17.51 ± 0.24	17.18 ± 0.22	16.72 ± 0.22	15.94 ± 0.22	<0.001
Alcohol (energy %)	2.76 ± 0.44	3.24 ± 0.37	2.61 ± 0.31	2.41 ± 0.26	0.401
Fiber (g/d)	27.4 ± 0.8	27.9 ± 0.7	28.1 ± 0.7	26.8 ± 0.9	0.704
EE in PA (kcal/d)	270.0 ± 20.7	281.5 ± 24.9	283.4 ± 21.5	310.2 ± 29.1	0.696

Data are mean ± SE, number (*n*) or percentage (%).
Abbreviations: BMI = body mass index; EE = energy expenditure; PA = physical activity.

observed across the quartiles of change in GI (Q1: −26.18 ± 55.79 kcal/d, Q4: 169.22 ± 49.64 kcal/d, *p* for trend = 0.039) and GL (Q1: −422.22 ± 39.3, Q4: 554.49 ± 42.06, *p* for trend < 0.001).

Discussion

The results of the cross-sectional analysis conducted in 511 elderly subjects show an inverse association between plasma leptin and adiponectin concentrations, and dietary GI and GL. Furthermore, in a prospective longitudinal assessment after a 1-year follow-up we demonstrated an inverse association between an increased dietary GI or GL and changes in both plasma leptin and adiponectin levels, independently of potential dietary and non-dietary confounders. However, no significant relationships were observed between dietary GI or GL and other adipokine metabolic markers analyzed.

High dietary GI and GL have been related with increased incidence of obesity, T2DM [5], and cardiovascular disease [5,6,22]. The most direct effect of a diet with high-GI and GL is the fast increase in postprandial glycemia and insulinemia. The induced hyperinsulinemia promotes glucose uptake by liver and muscle, while suppressing lipolysis in

Table 2 Inflammatory and obesity or diabetes risk markers according to glycemic index quartiles at baseline.

	Glycemic index quartiles				
	Q1	Q2	Q3	Q4	*p* ANOVA
	61.27 (60.49–62.05)	69.02 (68.75–69.28)	73.99 (73.72–74.26)	80.09 (79.63–80.54)	
Ghrelin (pg/mL)	12.42 (11.24–13.60)	12.66 (11.55–13.87)	13.30 (12.10–14.58)	13.63 (12.40–15.00)	0.509
GIP (pg/mL)	91.74 (82.68–101.90)	88.23 (79.83–97.91)	91.10 (82.18–100.98)	96.54 (82.18–107.77)	0.670
GLP (ng/mL)	1.29 (1.07–1.41)	1.11 (0.97–1.26)	1.20 (1.04–1.36)	1.40 (1.30–1.60)	0.127
IL-6 (pg/mL)	9.48 (8.23–10.94)	8.81 (7.68–10.12)	9.97 (8.67–11.47)	11.63 (10.08–13.40)	0.050
Leptin (ng/mL)	2.98 (2.74–3.25)	3.03 (2.80–3.30)	2.95 (2.73–3.22)	2.98 (2.74–3.24)	0.986
PAI-1 (ng/mL)	3.38 (3.18–3.56)	3.37 (3.18–3.56)	3.15 (2.95–3.32)	3.22 (3.04–3.42)	0.278
Resistin (pg/mL)	1.05 (0.97–1.14)	1.04 (0.96–1.13)	0.94 (0.88–1.04)	0.98 (0.91–1.06)	0.318
TNF (pg/mL)	11.82 (10.06–14.09)	11.25 (9.56–13.19)	12.89 (10.91–15.18)	15.56 (13.14–18.41)	0.046
Visfatin (ng/mL)	4.03 (3.32–4.88)	3.77 (3.14–4.54)	4.29 (3.53–5.16)	4.40 (3.64–5.41)	0.677
Adiponectin (μg/mL)	53.22 (44.90–63.08)	50.62 (42.71–59.41)	43.14 (36.39–51.13)	41.02 (34.62–48.64)	0.114
Adipsin (μg/mL)	1.11 (0.95–1.28)	1.12 (0.97–1.11)	0.96 (0.83–1.11)	1.02 (0.88–1.19)	0.411
A/L ratio	28.42 (23.82–33.20)	26.67 (22.13–31.22)	25.35 (20.64–30.06)	22.25 (17.56–26.95)	0.320

Metabolic markers values are expressed as geometric mean (CI 95%). Values were adjusted for sex, age, body mass index, waist circumference, physical activity in leisure time, smoking, insulin use, presence of type 2 diabetes mellitus, w-3 fatty-acid intake and fiber intake.
A/L ratio = adiponectin/leptin ratio.

Table 3 Inflammatory and obesity or diabetes risk markers according to glycemic load quartiles at baseline.

	Glycemic load quartiles				
	Q1	Q2	Q3	Q4	*p* ANOVA
	135.43 (128.61–142.26)	163.11 (155.70–170.53)	188.5 (178.91–198.22)	229.58 (217.02–242.13)	
Ghrelin (pg/mL)	12.42 (11.24–13.73)	12.67 (11.58–13.87)	12.67 (11.47–13.87)	12.67 (11.47–13.87)	0.292
GIP (pg/mL)	62.28 (73.69–92.57)	89.83 (80.04–9.68)	95.77 (86.31–106.27)	100.48 (89.12–112.28)	0.137
GLP (ng/mL)	1.17 (1.01–1.35)	1.16 (1.01–1.32)	1.23 (1.07–1.41)	1.36 (1.36–1.57)	0.447
IL-6 (pg/mL)	9.58 (8.21–11.20)	9.17 (7.97–10.56)	9.58 (8.37–11.11)	11.39 (9.79–13.25)	0.220
Leptin (ng/mL)	2.73 (2.49–2.98)	3.03 (2.80–3.30)	3.02 (2.78–3.28)	2.08 (2.92–3.49)	0.139
PAI-1 (ng/mL)	3.35 (3.15–3.58)	3.24 (3.06–3.44)	3.23 (3.05–3.42)	3.30 (3.05–3.51)	0.809
Resistin (pg/mL)	1.03 (0.94–1.13)	1.00 (0.92–1.08)	1.01 (0.94–1.09)	0.99 (0.90–1.07)	0.925
TNF (pg/mL)	12.55 (10.38–15.02)	11.47 (9.74–13.62)	12.21 (10.32–14.43)	15.16 (12.69–18.13)	0.161
Visfatin (ng/mL)	3.68 (2.98–4.54)	3.80 (3.15–4.60)	4.22 (3.50–5.10)	4.82 (3.95–5.90)	0.313
Adiponectin (μg/mL)	48.64 (39.82–60.55)	49.62 (39.82–58.82)	50.93 (42.92–60.36)	38.41 (31.99–46.13)	0.106
Adipsin (μg/mL)	1.03 (0.88–1.22)	1.04 (0.90–1.22)	1.12 (0.70–1.30)	1.01 (0.86–1.17)	0.792
A/L ratio	29.23 (24.16–34.31)	26.71 (22.08–31.34)	27.41 (22.76–31.05)	19.66 (14.69–24.63)	0.059

Metabolic markers values are expressed as geometric mean (CI 95%). Values were adjusted for sex, age, body mass index, waist circumference, physical activity in leisure time, smoking, insulin use, presence of type 2 diabetes mellitus, w-3 fatty-acid intake, fiber intake.
A/L ratio = adiponectin/leptin ratio.

adipoctyes and reducing the release of glucose from the liver into the circulation. As a result, blood glucose decreases rapidly, and hunger response occurs faster with a high-GI or GL than with a low-GI or GL diet [23].

It is quite clear that energy homeostasis requires a fine regulation of food intake, nutrient absorption, energy expenditure and storage. These processes are coordinated by the central nervous system after controlling the

Table 4 Mean changes in inflammatory and obesity or diabetes markers after 1 year in subjects in the 4 quartiles of glycemic index at baseline relative to the change in quartile 1.

	Quartiles of changes in glycemic index				
	Q1	Q2	Q3	Q4	*p*[a]
	−11.62 (−12.29 to −10.95)	−3.67 (−6.89 to −1.54)	0.78 (−1.49 to 3.46)	8.92 (3.59–27.60)	
Ghrelin (pg/mL)	0	0.31 (−1.91 to 2.54)	−1.17 (−3.40 to 1.05)	−1.69 (−3.91 to 0.54)	0.069
GIP (pg/mL)	0	−4.66 (−19.93 to 10.59)	−1.16 (−16.46 to 14.12)	−2.43 (−12.84 to 17.71)	0.662
GLP (ng/mL)	0	0.10 (−0.17 to 0.38)	0.01 (−0.29 to 0.26)	−0.09 (−0.37 to 0.19)	0.384
IL-6 (pg/mL)	0	1.48 (−1.75 to 4.71)	−0.19 (−3.45 to 3.05)	−1.14 (−4.39 to 2.10)	0.329
Leptin (ng/mL)	0	−0.34 (−0.71 to 0.15)	−0.55 (−0.92 to −0.19)	−0.39 (−0.87 to −0.26)	0.019
PAI-1 (ng/mL)	0	−0.39 (−0.66 to −0.12)	−0.36 (−0.63 to −0.09)	−0.16 (−0.43 to 0.10)	0.293
Resistin (ng/mL)	0	−0.09 (−0.20 to 0.01)	−0.09 (−0.20 to 0.02)	−0.08 (−0.21 to −0.03)	0.166
TNF (pg/mL)	0	2.84 (−2.43 to 8.12)	−0.62 (−5.92 to 4.67)	−1.42 (6.72–3.87)	0.367
Visfatin (ng/mL)	0	0.61 (−0.80 to 2.03)	0.16 (−1.27 to 1.60)	0.19 (−1.23 to 1.62)	0.959
Adiponectin (μg/mL)	0	−2.46 (−14.73 to 0.97)	−0.96 (−13.04 to 11.12)	−15.14 (−27.32 to −0.29)	0.027
Adipsin (μg/mL)	0	0.06 (−0.11 to 0.27)	0.11 (−0.06 to 0.28)	−0.12 (−0.29 to 0.03)	0.233
A/L ratio	0	1.34 (−7.39 to 10.08)	2.23 (−6.33 to 10.80)	−3.87 (−12.59 to 479)	0.461

Associations were calculated using a linear regression model. Values are mean differences (CI 95%) compared to Q1. Values were adjusted for sex, age, changes in waist circumference, changes in body mass index, intervention group, physical activity in leisure time, smoking, insulin use, presence of type 2 diabetes mellitus, w-3 fatty-acid intake and fiber.
[a] *p* for linear trend. A/L ratio = adiponectin/leptin ratio.

Table 5 Mean changes in inflammatory and obesity or diabetes markers after 1 year in subjects in the 4 quartiles of glycemic load at baseline relative to the change in quartile 1.

	Quartiles of changes in glycemic load				
	Q1	Q2	Q3	Q4	*p* for linear trend
	−87.21 (−235.9 to −44.26)	−23.07 (−43.71 to −6.00)	10.13 (−5.97 to 29.40)	68.52 (29.44−245.89)	
Ghrelin (pg/mL)	0	0.97 (−1.30 to 3.26)	−0.28 (−2.57 to 2.00)	−0.30 (−2.67 to 2.08)	0.548
GIP (pg/mL)	0	−6.35 (−21.79 to 9.08)	−2.88 (−18.40 to 12.63)	17.61 (1.52−33.69)	0.029
GLP (ng/mL)	0	0.025 (−0.26 to 0.31)	−0.10 (−0.38 to 0.18)	0.10 (−0.19 to 0.39)	0.713
IL-6 (pg/mL)	0	−0.61 (−3.92 to 2.70)	−1.80 (−5.13 to 1.53)	0.33 (−3.11 to 3.78)	0.969
Leptin (ng/mL)	0	−0.28 (−0.62 to 0.05)	−0.37 (−0.71 to −0.03)	−0.35 (−0.71 to 0.005)	0.030
PAI-1 (ng/mL)	0	−0.14 (−0.42 to 0.13)	−0.28 (−0.56 to −0.006)	−0.09 (−0.37 to 0.19)	0.368
Resistin (ng/mL)	0	0.01 (−0.05 to 0.17)	−0.07 (−0.18 to 0.04)	0.004 (−0.11 to 0.12)	0.483
TNF (pg/mL)	0	−0.04 (−5.45 to 5.36)	−2.49 (−7.93 to 2.94)	1.63 (−3.99 to 7.25)	0.798
Visfatin (ng/mL)	0	0.24 (−1.21 to 1.70)	−0.16 (1.63−1.30)	1.00 (−0.49 to 2.51)	0.282
Adiponectin (μg/mL)	0	−4.00 (−16.40 to 8.47)	−8.53 (−21.35 to 4.28)	−12.06 (−25.23 to 1.11)	0.054
Adipsin (μg/mL)	0	−0.01 (−0.18 to 0.15)	−0.06 (−0.23 to 0.11)	−1.43 (−0.32 to 0.03)	0.101
A/L ratio	0	2.37 (−6.42 to 11.57)	0.095 (−8.93 to 9.12)	−5.41 (−14.73 to 3.90)	0.206

Associations were calculated using a linear regression model. Values are mean differences (CI 95%) compared to Q1. Values were adjusted for sex, age, changes in waist circumference, changes in body mass index, intervention group, physical activity in leisure time, smoking, insulin use, presence of type 2 diabetes mellitus, w-3 fatty-acid intake and fiber.
A/L ratio = adiponectin/leptin ratio.

homeostatic signals derived from peripheral tissues. Since leptin discovered, the secretory activities of adipose tissue have increased exponentially with more than 50 adipocyte-derived products that make different contributions to obesity and its pathophysiological features [22]. Therefore, because a low grade of chronic inflammation is now recognized as one of the central mechanisms underlying obesity and associated comorbidities, the potential effect of dietary GI and GL on inflammatory modulation seems relevant. However, the few studies carried out to date are controversial because they focus on the plasma C-reactive protein and do not evaluate the long-term effects of GI or GL on adipostats or other adipokines related to obesity and comorbidities [9,13].

The results of our 1-year prospective longitudinal study conducted in a large sample of subjects at high cardiovascular risk are in agreement with the adipostatic theory. The adipokines, leptin and adiponectin, are considered to be the two major adipostats in humans because of their role in the central nervous system and in peripheral tissues [1,2]. In our study, we have demonstrated that an increase in the dietary glycemic index and glycemic load is associated with a decrease in leptin and adiponectin plasma concentrations. Our results are in agreement with those obtained using an intervention study conducted in rats fed with a high-glycemic index starch diet for 12 weeks [23] and those reported in a postprandial state [24]. Therefore, if we consider that higher leptin levels are associated with a decrease in food intake and an increase in energy expenditure acting at the hypothalamic central level [25], the down-regulation of leptin induced by an increase in GI or GL observed in our study could be considered as a mechanism favoring the weight gain and obesity attributed to high-GI diets. Moreover, because leptin also exerts autocrine or paracrine actions increasing lipolysis and decreasing lipogenesis, the decrease in circulating plasma leptin levels observed in our study may lead to a decrease in fatty-acid oxidation and an increase in glucose oxidation, which favors fat deposition. Finally, because leptin is primarily known as a satiety factor, the decrease in plasma leptin after a high-GI diet sustained the concept that these diets are less satiating than low-GI diets [26].

Adiponectin is the most abundant adipocytokine in humans. A low level of circulating adiponectin results in insulin resistance, glucose intolerance, dyslipidemia and atherosclerosis [27]. Recently, adiponectin has been identified in the cerebrospinal fluid of rodents suggesting that it has an important role in the central regulation of energy intake and energy expenditure [28]. However, although the central effects of adiponectin on energy balance are still unclear and controversial in humans [2] the results of our study support the hypothesis that high-GI-induced hypoadiponectinemia could be to the detriment of obesity. Moreover, the hypoadiponectinemia induced by the increase in dietary GI that we observed and reported in a previous epidemiologic study [12] could partly explain the relationship between the GI of the diet and the increased risk of T2DM and cardiovascular disease associated with the consumption of this type of diet.

In our study, we failed to show that the GI and GL had any relationship with incretins, other adipokines or related molecules. We only observed significantly higher levels of TNF and a trend to higher levels of IL-6 in those subjects in the higher GI quartiles, after adjusting for confounders, suggesting that pro-inflammatory cytokines worsened in

those subjects consuming high-GI foods. In a longitudinal manner, we also reported a positive relationship between an increase in GL and an increase in GIP, but not GLP-1, thus suggesting that a high dietary GL contributes to fat deposition and obesity.

The major strengths of the current study are that it carried out a longitudinal analysis of a large sample of individuals and measured a panel of adipokines and related molecules involved in energy metabolism, glucose metabolism and cardiovascular risk. However, we recognize several limitations. First, the study has been conducted in elderly subjects who are at high cardiovascular risk, and thus the results cannot be generalized to other populations. Second, potential dietary measurement error is a significant limitation. The FFQ used for dietary data collection was not designed to assess dietary GI and dietary GL, therefore both measurements are likely to have substantial errors. Moreover, due to scarcity of data, it was necessary to use GI values derived from studies conducted in different countries where the food or its properties may differ from that consumed in Spain. Nevertheless, these limitations would also apply to some other epidemiologic studies and clinical trials involving glycemic index and glycemic load measurements. Finally, our study was conducted in a cohort that was undergoing nutritional interventions, which might have had differential effects on peripheral adipocytokines. However, to address this limitation and to minimize the effect, we have adjusted all longitudinal analyses for the intervention group.

In conclusion, this study adds to the growing evidence that consumption of diets with high-GI foods or high dietary GL may modulate plasma concentrations of some cardiometabolic markers thus contributing to the promotion of obesity and cardiovascular disease. Additional research is necessary to evaluate these associations or effects on other populations and to explore the mechanisms leading to the interactions observed between dietary GI and GL, body weight and cardiovascular risk.

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Publication 3.

Title: Effect of the glycemic index of the diet on weight loss, modulation of satiety, inflammation and other metabolic risk factors: a randomized controlled trial.

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Abstract:

BACKGROUND: Low-GI diets have been proven to have beneficial effects in such chronic conditions as type 2 diabetes, coronary heart disease, and some types of cancer, but the effect of low-GI diets on weight loss, satiety, and inflammation is still controversial.

OBJECTIVE: We assessed the efficacy of 2 moderate-carbohydrate diets and a low-fat diet with different GIs on weight loss and the modulation of satiety, inflammation, and other metabolic risk markers.

DESIGN: The GLYNDIET study is a 6-mo randomized, parallel, controlled, clinical trial conducted in 122 overweight and obese adults. Participants were randomly assigned to one of the following 3 isocaloric energy-restricted diets for 6 mo: 1) a moderate-carbohydrate and high-GI diet (HGI), 2) a moderate-carbohydrate and low-GI diet (LGI), and 3) a low-fat and high-GI diet (LF).

RESULTS: At weeks 16 and 20 and the end of the intervention, changes in body mass index (BMI; in kg/m2) differed significantly between intervention groups. Reductions in BMI were greater in the LGI group than in the LF group, whereas in the HGI group, reductions in BMI did not differ significantly from those in the other 2 groups (LGI: 22.45 6 0.27; HGI: 22.30 6 0.27; LF: 21.43 6 0.27; F = 4.616, P = 0.012; pairwise comparisons: LGI compared with HGI, P = 1.000; LGI compared with LF, P = 0.016; HGI compared with LF, P = 0.061). The decrease in fasting insulin, homeostatic model assessment of insulin resistance, and homeostatic model assessment of b cell function was also significantly greater in the LGI group than in the LF group (P , 0.05). Despite this tendency for a greater improvement with a low-GI diet, the 3 intervention groups were not observed to have different effects on hunger, satiety, lipid profiles, or other inflammatory and metabolic risk markers.

CONCLUSION: A low-GI and energy-restricted diet containing moderate amounts of carbohydrates may be more effective than a high-GI and low-fat diet at reducing body weight and controlling glucose and insulin metabolism. This trial was registered at Current Controlled Trials (www.controlled-trials.com) as ISRCTN54971867.

See corresponding editorial on page 1.

Effect of the glycemic index of the diet on weight loss, modulation of satiety, inflammation, and other metabolic risk factors: a randomized controlled trial[1–3]

Martí Juanola-Falgarona, Jordi Salas-Salvadó, Núria Ibarrola-Jurado, Antoni Rabassa-Soler, Andrés Díaz-López, Marta Guasch-Ferré, Pablo Hernández-Alonso, Rafael Balanza, and Mònica Bulló

ABSTRACT

Background: Low–glycemic index (GI) diets have been proven to have beneficial effects in such chronic conditions as type 2 diabetes, ischemic heart disease, and some types of cancer, but the effect of low-GI diets on weight loss, satiety, and inflammation is still controversial.

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Design: The GLYNDIET study is a 6-mo randomized, parallel, controlled clinical trial conducted in 122 overweight and obese adults. Participants were randomly assigned to one of the following 3 isocaloric energy-restricted diets for 6 mo: *1*) a moderate-carbohydrate and high-GI diet (HGI), *2*) a moderate-carbohydrate and low-GI diet (LGI), and *3*) a low-fat and high-GI diet (LF).

Results: At weeks 16 and 20 and the end of the intervention, changes in body mass index (BMI; in kg/m^2) differed significantly between intervention groups. Reductions in BMI were greater in the LGI group than in the LF group, whereas in the HGI group, reductions in BMI did not differ significantly from those in the other 2 groups (LGI: -2.45 ± 0.27; HGI: -2.30 ± 0.27; LF: -1.43 ± 0.27; $F = 4.616$, $P = 0.012$; pairwise comparisons: LGI compared with HGI, $P = 1.000$; LGI compared with LF, $P = 0.016$; HGI compared with LF, $P = 0.061$). The decrease in fasting insulin, homeostatic model assessment of insulin resistance, and homeostatic model assessment of β cell function was also significantly greater in the LGI group than in the LF group ($P < 0.05$). Despite this tendency for a greater improvement with a low-GI diet, the 3 intervention groups were not observed to have different effects on hunger, satiety, lipid profiles, or other inflammatory and metabolic risk markers.

Conclusion: A low-GI and energy-restricted diet containing moderate amounts of carbohydrates may be more effective than a high-GI and low-fat diet at reducing body weight and controlling glucose and insulin metabolism. This trial was registered at Current Controlled Trials (www.controlled-trials.com) as ISRCTN54971867. *Am J Clin Nutr* 2014;100:27–35.

INTRODUCTION

Despite all the efforts of the scientific community and public health strategies, obesity is still one of the most important public health concerns and has been related to such comorbidities as hypertension, dyslipidemia, type 2 diabetes (T2D)[4], cardiovascular disease, and cancer (1). Current weight-management strategies have proposed physical activity, changes in diet, and changes in behavior as the keys to preventing and treating excess weight and obesity. Traditionally, these strategies have included energy-restricted diets with >50% of calories from carbohydrates, <30% of calories from fat, and the rest of calories from protein, but there is still no consensus on the role of the quality of the dietary macronutrient composition in long-term weight loss. A recent meta-analysis of randomized controlled trials that compared low-carbohydrate non–energy-restricted diets with energy-restricted low-fat (LF) diets showed that they were all equally effective for weight loss. However, low-carbohydrate diets were related to better improvements in the lipid profile (2). Nonetheless, in a pooled analysis that was based on observational studies, low-carbohydrate diets seemed to be associated with increased risk of all-cause mortality (3).

In 1998, the Food and Agriculture Organization of the United Nations suggested that the glycemic index (GI) of foods, which was a concept introduced by Jenkins et al (4) in 1981 to measure the quality of carbohydrates, could determine health status (5). Since then, several studies have evaluated the importance of

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[4] Abbreviations used: CRP, C-reactive protein; GI, glycemic index; GL, glycemic load; GLP-1, glucagon-like peptide-1; HGI, high glycemic index; HOMA-BCF, homeostatic model assessment of β cell function; ITT, intention to treat; LF, low fat; LGI, low glycemic index; PP, per protocol; RCT, randomized, controlled, clinical trial; T2D, type 2 diabetes; VAS, visual analog scale.

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dietary GI in different chronic conditions (6–9). However, the European Food Safety Authority has concluded that there is insufficient scientific evidence to recommend low–glycemic index (LGI) diets in the context of obesity treatment (10).

Physiologic mechanisms that relate high glycemic index (HGI) and body weight gain could be based on the postprandial metabolic environment precipitated by hyperglycemia and hyperinsulinemia, which accelerate glucose oxidation and stimulate fat storage. Even so, some authors have suggested that this relation is not of sufficient magnitude or duration to modify fuel oxidation (11). Satiety modulation also appears to be a potential mechanism that relates LGI and weight loss. Short-term satiety has been shown to increase in the vast majority of studies, although results have been inconsistent in long-term studies (12–14). Finally, few randomized clinical trials have been designed to evaluate the effect of GI or glycemic load (GL) on inflammation or related inflammatory markers (15–19). Most of these studies have been conducted in a reduced number of participants, have evaluated few biochemical markers, were of short duration, and usually did not control for other potential dietary confounders. For these reason, the precise role that dietary GI plays in inflammation is still controversial. We hypothesized that LGI diets exert a greater beneficial effect on weight loss than do HGI or traditional LF diets. The GLYNDIET study was a 6-mo randomized, controlled, dietary-intervention trial designed to assess the efficacy of 2 moderate-carbohydrate diets and an LF diet with different GIs on weight loss and the modulation of satiety, inflammation, and other metabolic risk markers.

SUBJECTS AND METHODS

Study population

The GLYNDIET study was designed as a 6-mo randomized, parallel, controlled, clinical trial with the aim of evaluating the effect of dietary GI on weight loss, satiety, glucose and insulin metabolism, lipid profile, inflammation, and other emergent metabolic risk markers. Full details of the GLYNDIET study protocol have been published elsewhere (20). Eligible participants were community-dwelling men and women aged between 30 and 60 y with BMI (in kg/m^2) between 27 and 35 who were recruited from 2010 to 2012. Participants were excluded if they had one of the following criteria: *1*) noncontrolled T2D defined as glycated hemoglobin >8%; *2*) systolic blood pressure >159 mm Hg or diastolic blood pressure >99 mm Hg; *3*) plasma LDL cholesterol concentration >160 mg/dL; *4*) plasma triglyceride concentration >400 mg/dL; *5*) suspicion of secondary obesity; *6*) presence of any inflammatory or chronic obstructive pulmonary disease, infection, active neoplastic, endocrine, or hematologic disease at the time of the study; *7*) blood leukocyte count $\geq 11 \times 10^6$ cells; *8*) use of anti-inflammatory drugs, steroids, hormones or antibiotics that could affect the variables analyzed in the study; *9*) changes in medication for lipid profile, diabetes, or hypertension in the previous 3 mo; *10*) active alcoholism or drug dependence, excluding tobacco use; *11*) a restrictive diet 3 mo before the study or weight loss >5 kg in the previous 3 mo; *12*) any medical condition that advised against being included in the study; and *13*) problems understanding the study or anticipated difficulty in making dietary changes according to the Prochaska and DiClemente model (21). Participants who fulfilled inclusion criteria were randomly assigned to 3 different dietary intervention groups of the same size. Random assignment was done by using a computer-generated, random-number sequence. Subjects were assigned to blocks of 3 participants balanced for sex, age (<45 and ≥45 y), and antidiabetic medication use (yes or no). The Institutional Review Board of the Sant Joan University Hospital (Reus, Spain) approved the study protocol on February 2009. All participants gave their written informed consent to participate in the study. This trial was registered at Current Controlled Trials (www.controlled-trials.com) as ISRCTN54971867.

Diets

The LGI and HGI diets had similar energy contents and macronutrient compositions but included foods with different GIs. GI values of each food were extracted from the International Glycemic Index, and GLs were determined by using glucose as the reference scale (22). The LF diet fulfilled the criteria defined by the American Heart Association (23). The total daily energy expenditure for each participant was estimated by using WHO (2001) equations and taking into account the estimated physical activity. Diets were designed at 1500, 1700, 2000, and 2500 kcal/d, and all participants were categorized as having one of the 4 categories of dietary energy content after subtracting 500 kcal/d of the total estimated energy intake to achieve a desired weight loss. Main characteristics of the diets used in the 3 intervention groups are shown in **Table 1**.

Anthropometric and biochemical measurements

Individual examinations were scheduled at baseline, 15 d into the intervention, and monthly until the end of the study. Laboratory technicians and statisticians were blinded to group assignments. Body weight and height were measured by using calibrated scales and a wall-mounted stadiometer with subjects wearing light clothes and no shoes. BMI was calculated. Waist circumference was measured twice midway between the lowest rib and the iliac crest. Body composition was measured by using a bioelectrical impedance analysis (TANITA TBF-300; Tanita), and we encouraged participants to void their bladders before all visits. Blood pressure was measured in the nondominant arm of each participant by using a validated semiautomatic oscillometer (Omron HEM-705CP; OMRON Corp) in duplicate with a 5-min interval between each measurement. Means of these values were recorded. Satiety was evaluated at baseline after a test meal by using visual analog scales (VASs). Physical activity was evaluated by using the validated Spanish version of the Minnesota Leisure Time Physical Activity Questionnaire (24). Blood samples

TABLE 1
Characteristics of diets[1]

	LGI diet (n = 41)	HGI diet (n = 40)	LF diet (n = 40)
Energy from protein (% of kcal)	18	18	18
Energy from carbohydrates (% of kcal)	42	42	52
Energy from total fat (% of kcal)	40	40	30
Glycemic index	34	62	65

[1] HGI, high glycemic index; LF, low fat; LGI, low glycemic index.

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were collected at baseline and end of the study. Plasma fasting glucose, serum total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride, and nonesterified fatty acid concentrations were determined by using standard enzymatic automated methods (COBAS; Roche Diagnostics Ltd). In subjects whose triglyceride concentrations were <400 mg/dL, LDL-cholesterol concentrations were estimated by using Friedewald's formula. Fasting insulin (Merck Millipore), oxidized LDL (Mercodia), total osteocalcin (DRGInstruments GmbH), and uncarboxylated osteocalcin (Takara Bio) were determined in plasma by using enzyme-linked immunosorbent assay commercial kits. All other metabolic biomarkers [ie, glucose-dependent insulinotropic polypeptide (gastric inhibitory polypeptide), glucagon-like peptide-1 (GLP-1), peptide YY, leptin, monocyte chemotactic protein-1, adiponectin, plasminogen activator inhibitor-1, soluble intercellular adhesion molecule 1, and soluble vascular cell adhesion molecule 1) were determined by using a MILLIPLEX MAP Plex Kit (Merck Millipore). Insulin resistance and secretion were estimated by using HOMA-IR and homeostatic model assessment of β cell function (HOMA-BCF) methods (25).

Dietary assessment

Dietary intake was estimated at baseline and first, third, and sixth months of the intervention by using 3-d dietary records that included 2 workdays and a weekend day. Energy and nutrient intake were calculated by using Spanish food-composition tables (26).

VASs

At baseline, a fixed breakfast test, according to the nutritional characteristics of the intervention-assigned diets, was served to all subjects (*see* Supplemental Table 1 under "Supplemental data" in the online issue). VASs were evaluated in a fasted state (immediately before the breakfast) and every 30 min after for a period of 2 h in a controlled environment. Appetite ratings consisted of questions regarding hunger, satiety, fullness, and desire to eat. Participants were instructed to consider the extremes of each rating as the most-intense sensation they could imagine. Questions included "How hungry do you feel now?" "How satiated do you feel now?" "How full do you feel now?" and "How strong is your desire to eat now?" and were accompanied by horizontal lines anchored at each end by the words "Not at all" and "Extremely."

Statistical analysis

Descriptive data of participants at baseline and differences between final and baseline visits for continuous measures are shown as means (±SEMs) or medians and IQRs. Descriptive data for categorical variables are shown as numbers and percentages. The normal distribution of variables was tested by using the Kolmogorov-Smirnov test. An ANOVA and ANCOVA were used to assess differences intervention groups both in anthropometric and biochemical variables, respectively, in those variables with a normal distribution. Changes in biochemical variables were adjusted for their baseline values. The Bonferroni post-hoc test was used for multiple comparisons. Variables without a normal distribution were analyzed by using the Kruskal-Wallis test for comparisons between intervention groups and the Mann-Whitney test for pairwise comparisons by applying Bonferroni correction. These variables were adjusted by baseline values of each variable by using the residual method (27). All statistical analyses were conducted by both intention-to-treat (ITT) and per protocol (PP) approaches. The ITT analysis included all randomly assigned participants. The last observation carried forward was used for handling missing data. The PP analysis excluded participants who did not attend the last visit (*see* Supplemental Tables 2 and 3 under "Supplemental data" in the online issue for results). A power analysis for ANOVA showed that a sample size of 33 participants was required for each group to detect a mean weight-loss difference similar to that published by other authors (28, 29), with an α error of 0.05, and a power of 0.90. All analyses were done with SPSS 19.0 software (SPSS Inc), and significance was defined as $P < 0.05$.

RESULTS

Study participants

The study flowchart is shown in **Figure 1**. A total of 543 participants were screened by telephone to identify 215 eligible participants. Of these individuals, 122 subjects met all inclusion criteria and were randomly assigned to one of the 3 intervention groups. During the intervention, 17 of 122 randomly assigned participants (14%) dropped out of the study. The dropout rate was lower in both LGI- and HGI-diet groups than in the LF-diet group (9.8% compared with 22.5%). One participant was finally excluded from the analysis because she decided to withdraw her informed consent, and she was not included in any of the analyses. Baseline characteristics of participants are shown in **Table 2**. At baseline, no significant differences were observed between intervention groups in sex, age, anthropometric measurements, blood pressure, or prevalence of comorbidities.

Diets

See Supplemental Table 4 under "Supplemental data" in the online issue for baseline and 6-mo changes in dietary variables. At baseline, study intervention diets were similar between groups, with the exception of percentage of energy coming from protein intake (mean ± SEM: 17.0% ± 0.4%, 18.8% ± 0.5%, and 18.4% ± 0.5% for LGI-, HGI-, and LF-diet groups, respectively; $P = 0.023$). After 6 mo, subjects in the LF-diet group showed significantly higher intake of carbohydrates and lower intake of fat than did subjects in the HGI- and LGI-diet groups ($P < 0.001$). Also, participants allocated to the LGI-diet group had significant lower dietary GI than did those allocated to HGI- and LF-diet groups ($P < 0.001$).

Total-body weight loss

In the ITT analysis, BMI decreased significantly throughout the 6-mo intervention in the 3 experimental groups (**Figure 2**). During the first 12 wk of intervention, no significant differences in body weight loss were observed between groups. At weeks 16, 20, and 24, decreases in BMI were higher in the LGI-diet group than in the LF-diet group (Figure 2). No significant changes in waist circumference (Figure 2) or body composition were observed between groups (changes in the percentage of fat-free mass with respect to changes in body weight were 41.5 ±

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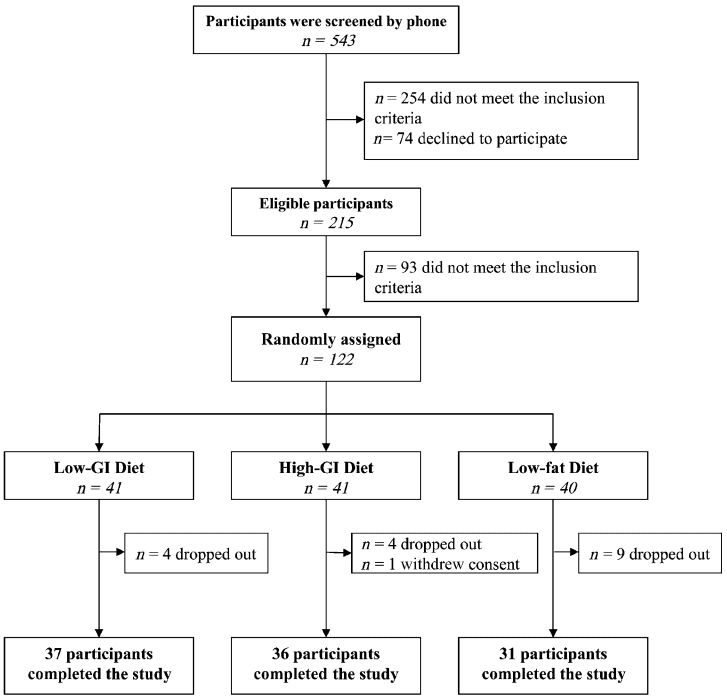

FIGURE 1. Flowchart of the study participants. GI, glycemic index.

8.4%, 37.9 ± 8.2%, and 43.7 ± 8.3% in the LGI-, HGI-, and LF-diet groups, respectively; $P = 0.879$).

The PP analysis included 104 participants who finished the study. After 6 mo of intervention, changes in BMI were higher in the LGI-diet group than in the LF-diet group ($P = 0.01$). Other anthropometric measurements were similar to those taken in the ITT analysis (*see* Supplemental Figure 1 under "Supplemental data" in the online issue).

Glucose metabolism and lipid profile

Mean (±SEM) values for glucose metabolism and lipid profile at baseline and 6-mo changes are shown in **Table 3**. Improvements in fasting insulin, HOMA-IR, and HOMA-BCF were greater in the LGI-diet group than in the LF-diet group. No significant differences were observed compared with the HGI-diet group. After adjustment for changes in BMI, the improvement in HOMA-BCF remained significant ($P = 0.03$), and changes in HOMA-IR were slightly attenuated ($P = 0.05$). Changes in lipid profile were not different between groups. PP results (*see* Supplemental Table 2 under "Supplemental data" in the online issue) were very similar to those shown by using the ITT approach.

Satiety, inflammation status, and other related markers

Baseline and 6-mo changes in satiety, inflammation status, and biomarkers of endothelial function are shown in **Table 4**. No

TABLE 2
Baseline characteristics of study participants[1]

Variable	LGI diet ($n = 41$)	HGI diet ($n = 40$)	LF diet ($n = 40$)	P
Sex (F) [n (%)]	33 (81)	33 (83)	31 (78)	0.853
Age (y)	42.5 ± 1.1[2]	44.0 ± 1.3	44.1 ± 1.3	0.603
Weight (kg)	82.7 ± 1.5	82.7 ± 1.6	83.5 ± 1.7	0.912
BMI (kg/m^2)	31.3 ± 0.3	30.8 ± 0.3	30.8 ± 0.3	0.544
Waist circumference (cm)	101.8 ± 1.2	100.0 ± 1.3	103.1 ± 1.1	0.204
Free fat mass (kg)	49.6 ± 1.2	50.3 ± 1.5	51.3 ± 1.6	0.721
Systolic blood pressure (mm Hg)	128.0 ± 2.7	128.0 ± 2.4	131.3 ± 2.2	0.555
Diastolic blood pressure (mm Hg)	80.2 ± 1.7	81.2 ± 1.5	82.8 ± 1.4	0.493
Hypercholesterolemia [n (%)]	3 (7)	2 (5)	5 (13)	0.459
Hypertension [n (%)]	7 (17)	5 (13)	5 (13)	0.791
Current smokers [n (%)]	8 (20)	5 (13)	5 (13)	0.591
Leisure-time physical activity (kcal/d)	205.5 ± 47.1	280.9 ± 47.2	200.0 ± 37.3	0.355

[1] P values of differences between intervention groups (ANOVA was used for continuous variables, and the chi-square test was used for categorical variables). HGI, high glycemic index; LF, low fat; LGI, low glycemic index.
[2] Mean ± SEM (all such values).

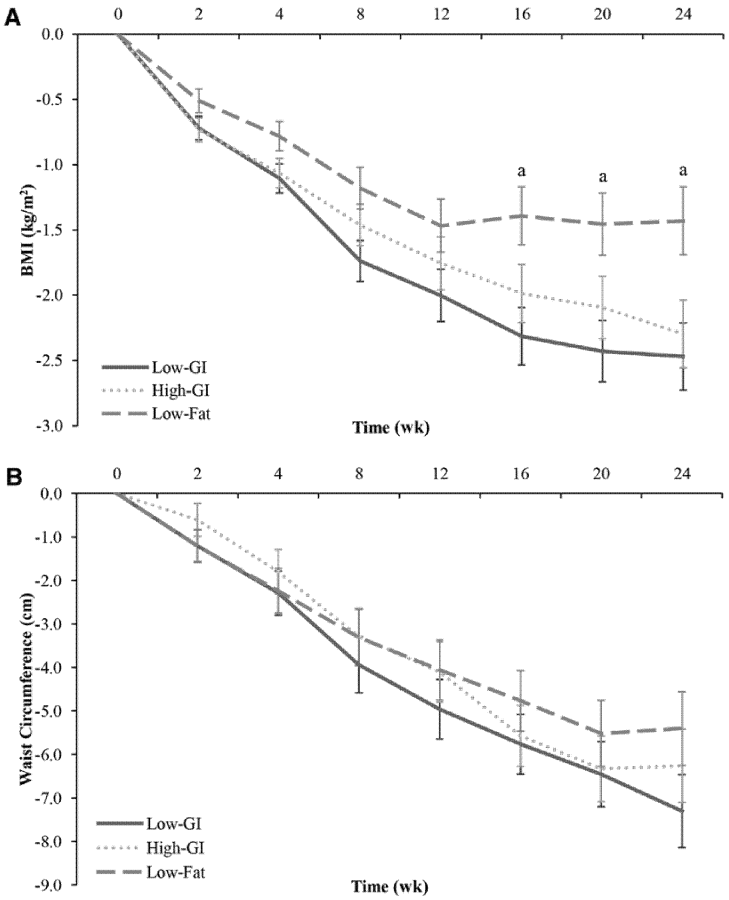

FIGURE 2. Changes in BMI (A) and waist circumference (B) during the 6-mo follow-up for each intervention group. Total $n = 121$. ANOVA models were used to assess differences between intervention groups. [a]$P < 0.05$ between low-GI and low-fat groups. The P value of changes in BMI at the end of the intervention was 0.012; pairwise comparisons: low-GI group compared with high-GI group, $P = 1.000$; low-GI group compared with low-fat group, $P = 0.016$; high-GI group compared with low-fat group, $P = 0.061$. GI, glycemic index.

significant differences were observed in baseline peripheral blood metabolic marker concentrations between groups. The exception was concentrations of adiponectin, which were lower in the LF-diet group. At 6 mo, a decrease in GLP-1 observed in the HGI-diet group differed from changes observed in the LF-diet group (median ± IQR: −1.65 ± 2.88 compared with 0.30 ± 3.28 pg/mL, respectively; $P = 0.028$). These differences were attenuated after adjustment for changes in BMI ($P = 0.144$; data not shown). Diets were not observed to have any significant effects on other biomarkers analyzed although they tended to improve throughout the intervention in the LGI diet. PP changes in metabolic risk markers were similar to those shown by using the ITT approach (*see* Supplemental Table 3 under "Supplemental data" in the online issue).

VASs

Subjective VAS measures for hunger and satiety (time-course and incremental AUC data) taken in 95 participants who answered all questionnaires are shown in **Figure 3**. Two hours after the breakfast, significantly greater reductions in hunger sensations were shown in subjects allocated to the LGI-diet group than in those allocated to the HGI-diet group (mean ± SEM: −4.13 ± 0.46 compared with −2.52 ± 0.45 cm, respectively; $P = 0.048$). No differences were shown between dietary interventions in subjective perceptions of hunger 2 h after the breakfast test. Subjective sensations of satiety in the 2 h after the breakfast study are shown in Figure 3. No differences were shown at any of the time points analyzed. The incremental AUC for subjective sensations of hunger and satiety were not significantly different between dietary intervention groups.

DISCUSSION

To our knowledge, this is the first study to simultaneously evaluate the effectiveness of moderate-carbohydrate LGI, moderate-carbohydrate HGI, and LF diets with weight loss as the main outcome. Results of the current randomized, controlled, clinical trial (RCT) showed that the LGI diet reduced weight more effectively than did a traditional LF diet. Moreover, the LGI diet led to a significantly greater improvement in insulin resistance and sensitivity than did the LF diet. LGI and HGI diets were not observed to have different effects on body weight and insulin metabolism. Postprandial satiety and hunger rates, lipid

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TABLE 3
Baseline and 6-mo changes in glucose metabolism metabolites and lipid profiles[1]

Variable	LGI diet (n = 41)	HGI diet (n = 40)	LF diet (n = 40)	P
Fasting plasma glucose (mg/dL)[2]				
Baseline	99.00 ± 10.00	98.00 ± 12.00	100.00 ± 16.50	0.312
6-mo change	−2.76 ± 13.00	−5.08 ± 18.25	−3.35 ± 10.00	0.575
Fasting plasma insulin (mU/mL)[3]				
Baseline	5.96 ± 0.49	4.44 ± 0.48	4.94 ± 0.49	0.091
6-mo change	−1.41 ± 0.34[4]	−1.10 ± 0.35	−0.09 ± 0.34	0.019
HOMA-IR[2]				
Baseline	1.20 ± 1.01	0.90 ± 0.69	1.07 ± 1.08	0.101
6-mo change	−0.62 ± 0.54[4]	−0.58 ± 0.33	−0.39 ± 0.42	0.009
HOMA-BCF[2]				
Baseline	55.18 ± 38.97	38.88 ± 33.33	40.51 ± 30.18	0.037
6-mo change	−11.78 ± 30.63[4]	−6.78 ± 18.09	−4.60 ± 21.13	0.022
Total osteocalcin (ng/mL)[3]				
Baseline	7.74 ± 0.54	8.56 ± 0.53	8.01 ± 0.53	0.548
6-mo change	1.90 ± 0.38	1.85 ± 0.39	1.08 ± 0.39	0.242
Uncarboxylated osteocalcin (ng/mL)[3]				
Baseline	7.09 ± 0.64	6.56 ± 0.63	6.63 ± 0.63	0.823
6-mo change	0.91 ± 0.41	0.35 ± 0.41	−0.43 ± 0.41	0.072
Total cholesterol (mmol/L)[3]				
Baseline	4.99 ± 0.13	5.13 ± 0.13	4.82 ± 0.13	0.203
6-mo change	−0.05 ± 0.11	0.13 ± 0.11	0.00 ± 0.11	0.485
HDL cholesterol (mmol/L)[3]				
Baseline	1.45 ± 0.05	1.47 ± 0.05	1.37 ± 0.05	0.248
6-mo change	0.03 ± 0.03	0.08 ± 0.03	0.05 ± 0.03	0.581
LDL cholesterol (mmol/L)[3]				
Baseline	3.05 ± 0.11	3.15 ± 0.10	2.95 ± 0.10	0.383
6-mo change	0.03 ± 0.08	0.14 ± 0.08	−0.02 ± 0.08	0.419
Oxidized LDL (mU/L)[3]				
Baseline	48.69 ± 2.21	50.60 ± 2.18	46.46 ± 2.19	0.408
6-mo change	−0.46 ± 1.64	−0.90 ± 1.67	−3.37 ± 1.67	0.413
Total-cholesterol:HDL-cholesterol ratio[3]				
Baseline	3.51 ± 0.11	3.59 ± 0.10	3.59 ± 0.10	0.827
6-mo change	−0.13 ± 0.05	−0.14 ± 0.05	−0.13 ± 0.05	0.992
LDL-cholesterol:HDL-cholesterol ratio[3]				
Baseline	2.16 ± 0.09	2.22 ± 0.09	2.20 ± 0.09	0.867
6-mo change	−0.04 ± 0.05	−0.05 ± 0.05	−0.09 ± 0.05	0.725
Triglycerides (mmol/L)[2]				
Baseline	1.00 ± 0.47	1.03 ± 0.70	0.98 ± 0.85	0.819
6-mo change	−0.27 ± 0.42	−0.26 ± 0.49	−0.25 ± 0.38	0.516
Nonesterified fatty acids (μmol/L)[3]				
Baseline	534.18 ± 30.92	490.04 ± 30.19	475.46 ± 30.31	0.390
6-mo change	−26.02 ± 25.15	−41.69 ± 25.11	−77.26 ± 25.14	0.340

[1] ANCOVA models were used to assess differences between intervention groups in variables with normal distributions, and the Kruskal-Wallis test was used in variables without normal distributions. Changes in biochemical variables were adjusted for baseline values of each biochemical variable. HGI, high glycemic index; HOMA-BCF, homeostatic model assessment of β cell function; LF, low fat; LGI, low glycemic index.
[2] Values are medians ± IQRs (variable without a normal distribution).
[3] Values are means ± SEMs.
[4] Significant difference compared with LF-diet group ($P < 0.005$).

profile, inflammation ,and related peripheral metabolic risk markers were similarly affected by the 3 dietary interventions.

Even though GI and GL modulation has emerged as a dietary alternative for the prevention or treatment of obesity, the effect of GI and GL on weight management remains controversial. A meta-analysis conducted on 6 RCTs with a total of 202 subjects who were randomly assigned to dietary interventions that ranged between 5 wk and 6 mo showed that LGI diets had a greater effect on weight loss (30) than did HGI or other control diets. Unfortunately, the studies did not adjust for potential confounders such as protein or total fiber. Recently, long-term effects of LGI compared with HGI diets have been assessed by a meta-analysis of 14 RCTs. Although the decrease in total body fat–free mass was significantly more pronounced after LGI diets, no significant changes were observed in weight and waist circumference between diets with a different GI or GL (31). In our study, subjects assigned to an LGI- or HGI diet lost more weight than did those in the LF-diet group, even after adjustment for potential dietary confounders. Our results suggested that diets rich in fat mainly derived from plant sources and with moderate amounts of carbohydrate, such as the Mediterranean Diet, are more effective at managing obesity than traditional LF diets are,

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TABLE 4
Baseline and 6-mo changes in satiety, inflammation, and other metabolic risk biomarkers[1]

Variable	LGI diet (n = 41)	HGI diet (n = 40)	LF diet (n = 40)	P
Gastric inhibitory polypeptide (pg/mL)[2]				
Baseline	23.71 ± 19.91	19.77 ± 16.58	23.11 ± 12.59	0.804
6-mo change	−5.66 ± 19.45	−7.67 ± 8.35	−5.41 ± 13.87	0.511
Glucagon-like peptide-1 (pg/mL)[2]				
Baseline	64.63 ± 16.25	64.23 ± 18.44	66.51 ± 14.23	0.944
6-mo change	−0.49 ± 4.11	−1.65 ± 2.88[3]	0.30 ± 3.28	0.028
Peptide YY (pg/mL)[2]				
Baseline	111.64 ± 20.41	110.40 ± 24.35	111.00 ± 23.96	0.531
6-mo change	−2.99 ± 7.19	−3.48 ± 9.24	−1.92 ± 5.55	0.231
Plasminogen activator inhibitor-1 (pg/mL)[4]				
Baseline	159.72 ± 10.84	170.66 ± 10.72	190.61 ± 10.76	0.133
6-mo change	−12.56 ± 7.74	−15.17 ± 7.81	−6.02 ± 7.87	0.700
C-reactive protein (μg/mL)[2]				
Baseline	2.99 ± 4.34	3.58 ± 6.25	3.70 ± 5.59	0.520
6-mo change	−0.19 ± 1.78	−0.07 ± 2.74	−0.04 ± 1.72	0.457
IL-6 (pg/mL)[2]				
Baseline	1.67 ± 1.18	1.36 ± 0.90	1.66 ± 1.11	0.324
6-mo change	−0.27 ± 0.86	0.12 ± 0.91	−0.01 ± 0.72	0.162
Leptin (ng/mL)[2]				
Baseline	14.47 ± 12.46	13.74 ± 10.36	13.01 ± 14.67	0.663
6-mo change	−5.64 ± 7.23	−6.03 ± 6.81	−3.75 ± 4.81	0.144
Monocyte chemotactic protein-1 (pg/mL)[4]				
Baseline	96.22 ± 4.33	95.78 ± 4.29	95.76 ± 4.30	0.997
6-mo change	−5.39 ± 3.01	−2.87 ± 3.05	−9.79 ± 3.05	0.271
Adiponectin (ng/mL)[2]				
Baseline	63.18 ± 71.84	69.97 ± 72.10	51.29 ± 44.02	0.020
6-mo change	1.95 ± 21.76	0.33 ± 26.89	0.24 ± 14.79	0.840
Intercellular adhesion molecule 1 (pg/mL)[2]				
Baseline	0.51 ± 0.25	0.57 ± 0.21	0.53 ± 0.25	0.375
6-mo change	0.01 ± 0.09	0.01 ± 0.14	0.02 ± 0.12	0.343
Vascular cell adhesion protein 1 (pg/mL)[4]				
Baseline	7.71 ± 0.26	8.23 ± 0.25	8.05 ± 0.25	0.364
6-mo change	0.19 ± 0.20	−0.07 ± 0.20	0.18 ± 0.20	0.592

[1] ANCOVA models were used to assess differences between intervention groups in variables with normal distributions, and the Kruskal-Wallis test was used in variables without normal distributions. Changes in biochemical variables were adjusted for baseline values of each biochemical variable. HGI, high glycemic index; LF, low fat; LGI, low glycemic index.
[2] Values are medians ± IQRs (variable without a normal distribution).
[3] Significant difference compared with LF-diet group ($P < 0.005$).
[4] Values are means ± SEMs.

irrespective of the quality of the carbohydrates determined by the GI. Nonetheless, the LGI diet had a slightly greater effect on body weight loss than did the HGI diet, which indicated that these diets can be used for clinical weight management.

In the current study, no differences were observed between diets in satiety or hunger rates derived from VASs, which suggested that the effect on body weight of LGI or HGI diets is mediated by other mechanisms rather than short-term satiety modulation. Despite this, and in line with results of short-term satiety studies (12), we observed a nonsignificant tendency to higher satiety rates and lower hunger rates in the LGI-diet group than in other groups.

Insulin sensitivity has been thought to have an important association with the effectiveness of GI on weight change (32). However, reports on the effect of dietary GI or GL on glucose and insulin metabolism have provided inconsistent data. Results of a recent systematic review and meta-analysis of RCTs showed no significant effects of diets with a different GI or GL on fasting glucose and glycated hemoglobin. However, the same meta-analysis showed that LGI diets had a significantly greater effect on fasting insulin than did HGI diets (31). In the GLYNDIET study, both insulin sensitivity and resistance significantly improved in participants in the LGI-diet group even after adjustment for changes in body weight, which suggested additional mechanisms that link GI and GL and insulin metabolism rather than body-weight reduction. Improvements in glycemia and insulinemia attributable to LGI diets could be mediated by changes in the incretin axis. In this regard, a 28-d weight-maintaining, HGL controlled diet led to significantly lower postprandial concentrations of GLP-1 than did a low-GL diet after a test breakfast (33). Results of our study support a long-term effect of GI on the incretin axis. However, the significant decrease in glucagon-like peptide-1 circulating concentrations observed in the HGI-diet group could explain the higher decrease of glucose concentrations observed in the same dietary intervention group. Additional research is needed to understand the exact long-term effect of GI and GL on the incretin axis and its implication in obesity and T2D. Because of the postulated effect of both osteocalcin and uncarboxylated osteocalcin forms on insulin resistance (34), the slightly higher increase in osteocalcin and uncarboxylated

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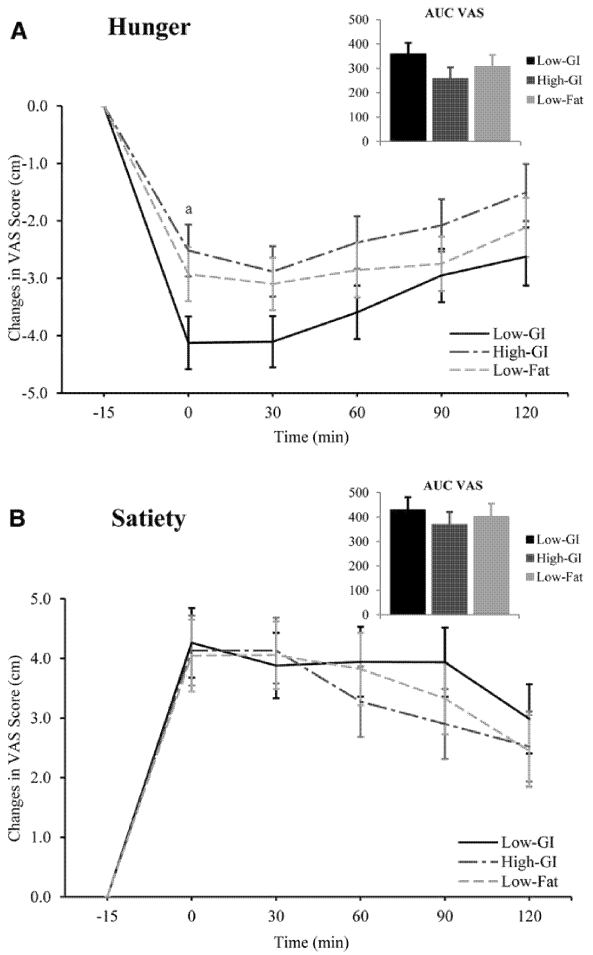

FIGURE 3. Subjective VAS measures for hunger (A) and satiety (B) after a breakfast meal for each intervention group measured in 95 participants. ANOVA models were used to assess differences between intervention groups. [a]$P < 0.05$ between low-GI and high-GI groups. GI, glycemic index; VAS, visual analog scale.

osteocalcin in the LGI-diet group than HGI- or LF-diet groups observed in our study reinforced the beneficial role that this type of diet plays in insulin metabolism. Overall, our results are in line with those of a previous meta-analysis (32) and support findings from prospective cohort studies that consistently indicated that the consumption of lower GI are associated with lower T2D risk (7). As expected, we observed that HDL cholesterol tended to increase, and triglycerides slightly decreased, although differences observed between groups were NS.

Inflammatory modulation has also been postulated as a potential mechanism that links dietary GI and GL with the management of obesity and its related comorbidities, although both observational and intervention studies have reported inconsistent data. Moreover, few clinical trials have evaluated the effect of GI and GL on inflammatory markers, and most studies have focused on C-reactive protein (CRP) (15–19). In 773 obese adults from the Diet, Obesity, and Genes trial, changes in CRP were significantly greater in LGI- than HGI-diet groups (19). Decreased IL-6, TNF-α, plasminogen activator inhibitor-1, and leptin concentrations have also been observed after weight loss induced by LF or LGI hypocaloric diets with no between-group differences (35). In our study, subjects allocated to the LGI-diet group show a significant reduction in peripheral CRP and leptin concentrations and a tendency to a higher decrease in IL-6 after the intervention. However, changes were shown to be different between intervention groups. In our study, the GI and GL of the diet were not observed to have any effect on the other inflammatory markers analyzed although, as expected, most of markers tended to improve because of the weight loss in all intervention groups.

Among the strengths of this study were its medium-term duration; randomized design balanced in each intervention group for sex, age, and use of T2D drugs; and differences between diets in relation to GI and GL. Moreover, to our knowledge, our trial is the first study to simultaneously analyze the effect of LGI, HGI, and LF diets on weight loss, satiety, glucose and insulin metabolism, and several associated metabolic risk markers.

There were also some study limitations. First, because the study has been conducted in a Mediterranean country, dietary fat sources were derived mainly from vegetable foods. Therefore, both LGI and HGI diets were rich in vegetable fatty acids, which limited the generalizability of our results to non-Mediterranean populations.

Second, our findings should not be generalized to obese people with obesity-related diseases (eg, T2D) who were not represented in our study subjects. Finally, we used dietary food records during the follow-up as an indirect marker of dietary compliance. A lack of specific biochemical markers of dietary compliance related to GI and GL was also a limitation of the study.

In conclusion, we showed that following a moderate-carbohydrate, LGI diet may be more effective for weight loss than a moderate-carbohydrate, HGI diet or a conventional LF diet. Metabolic benefits observed for insulin resistance and sensitivity in subjects who were consuming an LGI diet and the tendency to improve other inflammatory and associated metabolic risk markers also indicated that LGI diets are better tools for managing obesity and its associated comorbidities. Additional insights into this topic require additional studies to focus on mechanisms linking GI with body weight control.

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The authors' responsibilities were as follows—MB and JS-S: contributed to the conception, design, and implementation of the project; MJ-F, NI-J, AD-L, MG-F, AR-S, PH-A, RB, and MB: contributed to data collection and analytical procedures; MJ-F, JS-S, and MB: conducted the statistical analysis, interpreted data, and wrote the manuscript; and all authors: read and approved the final version of the manuscript. None of the authors had a personal or financial conflict of interest.

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Publication 4.

Title: Dietary glycemic index and glycemic load are positively associated with risk of developing metabolic syndrome.

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Abstract:

BACKGROUND/OBJECTIVES: The MetS is a cluster of metabolic abnormalities that have been associated with an increased risk of cardiovascular disease. The aim of the present study was to evaluate how the GI and GL are associated with MetS and its features.

SUBJECTS/METHODS: A prospective cohort analysis was conducted in 6,622 participants from the PREDIMED study. Energy and nutrient intakes were evaluated using a validated 137-item food frequency questionnaire. Dietary GI and GL were calculated using the international GI and GL values. MetS and its features were defined in accordance with the criteria of the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI).

RESULTS: In a cross-sectional analysis, a positive association was observed across tertiles of GI and MetS, abdominal obesity, hypertriglyceridemia, low HDL-cholesterol and high blood pressure features among non-diabetic participants (P for trend < 0.05) while no relationship was found between tertiles or the continuous variables of dietary GI or GL at baseline and the prevalence of MetS or any of its features among diabetic participants. During the median follow-up of 4.8 years, subjects in the third tertile of change in GI and GL have a greater risk of developing MetS than those in the first tertile (Hazard Ratio: 1.19, 95% CI: 1.01–1.40, P for trend= 0.05; Hazard Ratio: 1.23, 95% CI: 1.03–1.48, P for trend= 0.070) independently of the presence of diabetes. Changes in dietary GI were also associated with an increased risk of low HDL-cholesterol and high blood pressure MetS fe zatures. Changes in dietary GL were also associated with an increased risk of abdominal obesity, hypertriglyceridemia and low HDL-cholesterol.

CONCLUSIONS: Our results suggest that both dietary GI and GL have a potential role in the development of MetS and associated clinical features in subjects at high cardiovascular risk.

Dietary glycemic index and glycemic load are positively associated with risk of developing metabolic syndrome in elderly subjects

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Abbreviated title: Glycemic index and load, and Metabolic Syndrome

Abstract

Background: The metabolic syndrome (MetS) is a cluster of metabolic abnormalities that have been associated with an increased risk of cardiovascular disease. The aim of the present study was to evaluate how the glycemic index (GI) and glycemic load (GL) are associated with MetS and its features in elderly subjects.

Methods: A prospective cohort analysis was conducted in 6,622 elderly participants from the PREDIMED study. Energy and nutrient intakes were evaluated using a validated 137-item food frequency questionnaire. MetS and its features were defined in accordance with the criteria of the American Heart Association/National Heart, Lung, and Blood Institute.

Results: A positive association was observed across tertiles of GI and MetS, abdominal obesity, hypertriglyceridemia, low HDL cholesterol and high blood pressure features among non-diabetic participants ($P<0.05$) while no relationship was found among diabetic participants. During the median follow-up of 4.8 years, subjects in the third tertile of change in GI and GL have a greater risk of developing MetS than those in the first tertile (HR: 1.19, 95%CI: 1.01–1.40, P for trend= 0.05; HR: 1.23, 95%CI: 1.03–1.48, P for trend= 0.070) independently of the presence of diabetes. Changes in dietary GI were also associated with an increased risk of low HDL-cholesterol and high blood pressure. Changes in dietary GL were also associated with an increased risk of abdominal obesity, hypertriglyceridemia and low HDL-cholesterol.

Conclusions/interpretation: Our results suggest that both dietary GI and GL have a potential role in the development of MetS and associated clinical features in elderly subjects at high cardiovascular risk.

Trial registration: ISRCTN35739639

Keywords: Glycemic index, Glycemic Load, Metabolic Syndrome, Cardiovascular disease, PREDIMED.

Background

The prevalence of the metabolic syndrome (MetS) – a cluster of metabolic abnormalities including central obesity, hyperglycemia, hypertension and atherogenic dyslipidemia – has dramatically increased worldwide [1,2]. Among the mechanims underlying the development of the MetS, modern lifestyle and its associated physical inactivity and unhealthy have been pointed out as the main responsibles. A higher prevalence of MetS has been associated not only with the global epidemic of obesity and type 2 diabetes (T2DM) [3–5] but also with an increased risk of cardiovascular disease and all-cause mortality [6].

It has been proposed that high glycemic index (GI) and high glycemic load (GL) diets are associated with increased risks of obesity, T2DM, metabolic syndrome and cardiovascular disease [7–10]. Several observational studies have shown that dietary GI or GL are inversely associated with HDL cholesterol [11–13]. A positive association with TG has also been demonstrated [14–16]. It has also been reported that low-GI/GL diets can lower the risk of T2DM [8,17,18]. In a meta-analysis of 13 prospective cohort studies, subjects with the highest dietary GI and GL had a 16% and 20% greater risk of T2DM than the participants with the lowest dietary GI and GL, respectively [18]. Furthermore, dietary intake of high-GI foods has been associated with an increased BMI and waist circumference, and with an increased risk of obesity or central obesity [19–22].

The results of several prospective studies who assessed the association between GI/GL and the prevalence of metabolic syndrome are limited and inconsistent [10,23–25]. Whereas two studies have assessed a positive association between high-GI or GL and the prevalence of MetS [10,25], others have not been able to find any significant association [23,24]. These inconsistence observed between the current studies could be explained by differences between dietary intake assessment tools and different MetS criteria. To the best of our knowledge, no studies have evaluated the effect of dietary GI or GL on the incidence of MetS.

Therefore, the present study aimed to evaluate, the associations between dietary GI and GL and the prevalence and incidence of MetS and its features in a Mediterranean population at high cardiovascular risk.

Methods

The PREDIMED study (Prevención con Dieta Mediterránea) is a large, parallel group, multicenter, controlled, randomized clinical trial (RCT), aiming to assess the effect of Mediterranean diets on the primary prevention of cardiovascular disease in elderly subjects at high cardiovascular risk. A more detailed protocol of the PREDIMED study has been published elsewhere [26,27]. Participants were elderly men and women, 55–80 and 60–80 years of age, respectively, with no cardiovascular disease at enrolment and who had either T2DM or three or more of the following cardiovascular risk factors: smoking (>1 cig/day during the last month) , hypertension (systolic BP>=140 or diastolic BP>=90 mmHg or under antihypertensive medication), LDL-cholesterol>=160 mg/dl , high-density lipoprotein cholesterol level ≤ 40 mg/dL, overweight or obesity [Body mass index (BMI) ≥ 25 kg/m2] or family history of premature cardiovascular disease. The exclusion criteria were severe chronic illness, drug or alcohol addiction, history of allergy or intolerance to olive oil or nuts, or a low predicted likelihood of changing dietary habits according to Prochaska and DiClemente's stages-of-change model [28]. The 7447 elderly participants included in the study were randomly assigned in a 1:1:1 ratio to one of three nutritional education interventions: a Mediterranean diet supplemented with extra-virgin olive oil (approximately 1 litre per week); a Mediterranean diet supplemented with 30g of mixed nuts daily (15g of walnuts, 7.5 g of hazelnuts and 7.5 of almonds); or a control group in which participants received counselling so that they could follow a low-fat diet (20-30% E from fat). The protocol was approved by the institutional review boards at all study locations and subjects provided written informed consent.

Dietary assessment

A validated 137-item food frequency questionnaire (FFQ) was administered by trained dieticians at baseline and annually thereafter to the end of the study [29]. Energy and nutrient intake was calculated from Spanish food composition tables [30,31]. With glucose as a reference scale, GI values for each food were extracted from the international glycemic index and glycemic load values

[32]. The total dietary GL of each food was calculated by multiplying the quantity of each food item consumed per day by the amount of carbohydrate contained in a specified serving size of the food and the corresponding GI value. Dietary GI was then determined by dividing GL by total available carbohydrate intake and multiplying the result by 100 [33]. Reproducibility and relative validity of a self-administered FFQ used in the study was validated for dietary GI and GL (unpublished data). A total of 158 independent individuals (seventy-three men and eighty-five women) aged between 55 and 80 years old and from three different Spanish areas (Tarragona, Pamplona and Valencia) of the PREDIMED Study were evaluated. The FFQ was administered twice to explore reproducibility at 1 year and four 3-day dietary records were used as reference to explore validity. The data used for the validation of GI and GL was the same data used in the validation of the FFQ [29]. Reproducibility and relative validity for dietary GI explored by the intraclass correlation coefficient was 0.321 and 0.244, respectively, and 0.846 and 0.525 for dietary GL. Although the relative validity for GI was slightly low, intraclass correlation was highly significant (<0.0001) and similar with other studies [34].

Metabolic syndrome

Prevalent MetS and its features were defined in accordance with the updated harmonized International Diabetes Federation and the American Heart Association/National Heart, Lung, and Blood Institute criteria [35]. Participants were considered to have MetS if they had three or more of the following features: a) abdominal obesity for European individuals (≥88 cm and ≥102cm in women and men, respectively), b) hypertriglyceridemia [≥150 g/dL] or drug treatment for elevated TG, c) low concentrations of HDL-cholesterol [<40 mg/dL in men; <50 mg/dL in women] or drug treatment for low HDL-cholesterol, d) high blood pressure (systolic ≥130 and/or diastolic ≥85 mmHg) or antihypertensive drug treatment, e) high fasting glucose [≥100 mg/dL] or drug treatment

for diabetes. Subjects were diagnosed as MetS when they fullfill at least three diagnostic criteria, even if not all features of the MetS were obtained.

Anthropometric, biochemical and lifestyle measurements

Baseline weight and height were measured by trained personnel with calibrated scales and a wall-mounted stadiometer, respectively. Waist circumference was measured with an anthropometric tape midway between the lower rib and the superior border of the iliac crest. For BP measurement, participants rest quietly for five minutes in the seated position. A validated semi-automatic sphygmomanometer (Omron HEM-705CP) was used for the PREDIMED trial. An appropriate sized cuff was applied after measurement of arm circumference. A pulse obliteration pressure was obtained. At each visit, 3 measurements were obtained, separated by 2 minutes. The average of second and third measurement was written in the data collection form. If both measurements differ more than 5 mmHg, the whole procedure was repeated and additional BP readings were averaged. Leisure-time physical activity was evaluated using the validated Spanish version of the Minnesota leisure-time physical activity questionnaire [36]. Samples of serum and EDTA plasma were coded, shipped to central laboratories, and stored at −80°C until analysis. Centralized laboratory analyses (Clínic Hospital, Barcelona, Spain) were performed on frozen serum samples obtained in fasting conditions. Plasma glucose, serum cholesterol, high-density lipoprotein cholesterol, and triglyceride concentrations were determined using standard enzymatic automated methods. In patients whose TG concentrations were less than 400 mg/dL, low-density lipoprotein cholesterol concentrations were estimated using the Friedewald formula [37].

Statistical analysis

The baseline characteristics of study participants are given as a mean ±SD or as a percentage (%). Subjects who were outside the predefined values for total energy intake (>4000 or <800 kcal per day in men and >3500 or <500 kcal per day in women, using the criteria suggested by Willet [38])

were excluded from the analysis. Dietary GI and GL were divided into tertiles depending on the outcome variable of the analysis. Continuous variables of dietary GI and GL were expressed as 5 and 10 point increments, respectively. Interaction tests for sex, T2DM, and intervention group (sex x GI, T2DM x GI, intervention group x GI) (sex x GL, T2DM x GL, intervention group x GL) were analysed. Because the interaction between the presence of T2DM and baseline dietary GI was significant, the prevalence of MetS was analysed by dividing the population by the prevalence of T2DM. There was no interaction between GI/GL and the rest of the variables analysed. Logistic regression models were used to estimate the odds ratios (OR) and 95% confidence intervals (CI) so that the associations between dietary GI, GL, and prevalent MetS and its features could be evaluated. Tests for linear trend were performed by modelling the median values of dietary GI and GL tertiles as continuous variables. Additionally, a fully adjusted model was used with sex (men/women), age (years), BMI at baseline (kg/m^2), recruiting centre, tobacco use (never smoker, current smoker, former smoker), education (primary education, secondary education, graduate/academic) leisure-time physical activity (MET-min/d), Mediterranean diet score (continuous), total energy intake (kcal/d), alcohol intake (continuous, adding a quadratic term) and quintiles of dietary fiber, total fat and protein intakes as a covariates. Statistical models with GI as the independent variable were additionally adjusted for total energy intake, and statistical models with MetS as the outcome were also adjusted for all MetS features at baseline. The time variable used was the interval between the baseline measurement date and the date of the last follow-up, death or outcome diagnosis, whichever occurred first. Cox proportional hazards regression models were fitted to estimate hazard ratios (HR) and the corresponding 95% CIs for MetS incidence or each of the specific defining criteria (abdominal obesity incidence, hypertriglyceridemia incidence, low-HDL cholesterol incidence, high blood pressure incidence and high blood glucose incidence). To reduce within-person variability and represent long-term dietary intakes, changes in dietary GI

and GL were calculated using the differences between baseline values and the mean GI/GL of all the preceding visits (excluding baseline values) before the incidence of MetS. Changes in dietary GI and GL were categorized into tertiles, with the lowest tertile as the reference category. The intervention group was additionally used as a covariate in the fully adjusted model together with the other variables used in the logistic regression models. All analyses were made using SPSS 19.0 (SPSS Inc, Chicago, IL), and significance was defined as $P < 0.05$.

Results

We excluded 153 participants from the present study because their total energy intake was outside the predefined limits, 78 because their dietary data were not complete at baseline and 594 because MetS diagnosis at baseline was unknown. Thus, the total sample considered for the cross-sectional analysis was 6,622 participants, whereas the longitudinal assessment contained only those subjects free of MetS at baseline (n=1832). The longitudinal analysis of individual features of the metabolic syndrome contained all subjects free of each specific component at baseline. The general characteristics of the study participants are presented by GI and GL tertiles in **Table 1**. Participants in the highest tertile of dietary GI were more likely to be obese young men, smokers, with higher mean waist circumference, and with a lower mean Mediterranean diet score. Participants in the third GL tertile were more physically active and had a lower BMI than those in the lower tertile. **Table 2** shows the baseline dietary characteristics according to the GI and GL. As expected, energy intake was 14% and 35% higher in the upper tertiles of GI and GL, respectively. The dietary intake of carbohydrates and cereals was also significantly higher in the third tertiles of GI and GL. Dietary intake of fruit, vegetable and dairy products increased across GI tertiles but decreased across GL tertiles.

Tables 3 and 4 show the multivariate-adjusted OR for MetS prevalence and all of its features according to dietary GI and GL (as categorical and continuous variables) at baseline in non-diabetic and diabetic participants. Non-diabetic participants in the highest tertile of GI had a greater risk of prevalence of MetS (OR: 1.33; 95%CI: 1.09–1.63, P for trend=0.005), abdominal obesity (OR:1.44; 95%CI: 1.08-1.93, P for trend=0.014), hypertriglyceridemia (OR:1.24; 95%CI: 1.01-1.52, P for trend=0.045), low HDL-cholesterol (OR:1.27; 95%CI: 1.02-1.59, P for trend=0.034) and high blood pressure (OR:1.55; 95%CI: 1.01-2.39, P for trend=0.044) than those in the lowest tertile. Results were similar when GI was analysed as a 5-point increase. No significant associations were found

between high fasting glucose and GI expressed either as tertiles or as continuous variables. Higher risk of MetS and hypertriglyceridemia was observed with a 10-point increase in dietary GL (**Table 3**). In contrast, no significant associations were observed between GI or GL and the risk of MetS and its features among diabetic participants (**Table 4**). Even after adjusting for diabetes medication, the associations between GI (T3 vs.T1; OR: 1.16; 95%CI: 0.87-1.54) and GL (T3 vs.T1; OR: 0.93; 95%CI: 0.61-1.42), and MetS were very similar. Neither was any significant associations found with the other features of the MetS.

In a median follow-up of 4.8 years (interquartile range, 2.8 to 5.8), 931 participants developed MetS. In the assessment of the risk to develop MetS analysing 1832 participants free of MetS at baseline (**Table 5**), those participants in the upper tertile of GI change had a greater risk of developing MetS than those in the first tertile (HR: 1.19; 95%CI: 1.01–1.40; P for trend= 0.050). Similar statistically significant associations were also found with the 5-point increase continuous variable (HR: 1.10; 95% CI: 1.01–1.19, P=0.035). A marked increased risk of developing the low HDL-cholesterol component of the MetS (HR: 1.05; 95%CI: 1.02–1.09; P= 0.008) and high blood pressure (HR: 1.22; 95%CI: 1.07–1.40; P for trend= 0.027) was also observed with increasing GI. No significant associations were found with the other features of the MetS.

Furthermore, a significant increased risk of incidence of MetS, abdominal obesity, hypertriglyceridemia and low HDL cholesterol was found in those subjects in which GL increased the most. Participants in the third tertile of GL change had a 23% greater risk of MetS incidence, a 38% greater risk of abdominal obesity and a 36% greater risk of low-HDL cholesterol features of the MeS than those in the first tertile ($p<0.05$). Also, a 10-point increase in GL was associated with a higher risk of developing hypertriglyceridemia (HR: 1.04; 95%CI: 1.01–1.07, P=0.005). No significant association was demonstrated between changes in GL during the follow-up and high blood pressure or high fasting glucose incidence.

Discussion

In the present longitudinal study, we have demonstrated for the first time that an increase in dietary GI and GL during follow-up is associated not only with a higher risk of developing the metabolic syndrome but also with a higher risk of developing hypertrygliceridemia, abdominal obesity or low HDL-cholesterol concentrations, thus supporting a deleterious effect of high-GI or high-GL diets on the development of the metabolic syndrome in elderly subjects.

The association between overall dietary GI and GL, and disease risk has long been inconsistent across different studies. However, the results of a meta-analysis including 37 prospective cohort studies concluded that high-GI or GL diets independently increased the risk of T2DM, cardiovascular disease or some types of cancer [39]. To date, the potential protection offered by low-GI or GL diets on the metabolic syndrome has not been evaluated, and the results of the few cross-sectional studies that have been conducted on this issue have been inconsistent [10,23–25]. Although two studies have reported a positive association between high-GI or GL and the prevalence of MetS [10,25], others have not been able to find any significant association [23,24]. In our study, we have found a significant association between both dietary GI and GL and MetS or its features among non-diabetic participants, whereas no association was found in diabetic participants. These discrepancies between subjects could be explained by differences in the type and the amount of carbohydrates consumed as stated by less diabetic subjects in the highest tertile of GI and GL at baseline. More interestingly, increasing GI or GL during the follow-up was related with a greater risk of developing MetS, which suggests a causal relationship between carbohydrate quality and metabolic syndrome development.

One of the potential uses of dietary GI has been the management of body weight and fat distribution. The conclusion of two meta-analyses assessing this issue reported contradictory results. Whereas a significant weight-loss related to low-GI diets was observed in short-term

clinical trials [17], no beneficial effects were observed in the long term [40]. The differences observed between the two meta-analyses could be partly explained by the different follow-up time of the interventions. Moreover, these diets have not been included in the nutritional recommendations of the European Food Safety Authority in the context of obesity treatment [41]. The results on abdominal obesity are also far from conclusive. Whilst some observational studies have reported a positive relationship between GI and abdominal obesity [10,19], and a significant increase of 0.26 cm of waist circumference per year for a 10-unit increase in GI was observed in a cohort of 89,432 European adults [21], other studies have not found any relationship [23,24,42]. Additionally, a recent meta-analysis of randomized clinical trials with a follow up of at least 6 month reported no significant effect of GI/GL on waist circumference [40]. In the present study, non-diabetic participants in the highest GI tertile showed a large waist girth, thus contributing to the higher prevalence of MetS observed. Accordingly, in the longitudinal assessment the higher risk of developing abdominal obesity observed in those participants who increased their GL during the follow-up reinforces the potentially negative effect of these diets on such an important metabolic cardiovascular factor as abdominal obesity.

In agreement with previous findings [16,43,44], we also found a significant association between the highest GI tertile and blood pressure in non-diabetic subjects. Moreover, we found that the risk of developing hypertension increased with the increase in GI during the follow-up and a trend with increased GL at the limit of statistical significance. These longitudinal results support those published by Philippou et al. who reported significantly higher reductions in 24-h blood pressure after a 6-month low glycemic index diet in comparison to a high-GI diet [44]. This may be because increased insulin resistance, plasma cholesterol and abdominal obesity, all features of the MetS, act directly on the arterial wall [45] and as potential mediators of sodium retention and volume

expansion thus increasing both blood pressure [46,47] and inflammation, and affecting the oxide nitric system [48].

High dietary GI or GL have also been associated with lower concentrations of HDL cholesterol and increased concentrations of tryglycerides [11–13]. In a cross-sectional study of more than 18,000 non-diabetic middle-aged and older women, those in the highest quintiles of both GI and GL showed lower HDL-cholesterol concentrations and significantly higher TG concentrations [13]. Frost et al. also reported similar results in a cohort of British subjects [12]. However, in a recent meta-analysis of randomized clinical trials with at least a 6-month follow-up, GI/GL were not observed to have a significant effect on HDL cholesterol concentrations [40]. In our study, we also found an inverse association between GI or GL and low HDL-cholesterol and a positive association with hypertriglyceridemia in non-diabetic subjects. Moreover, subjects who increased their dietary GI or GL during the follow-up also showed a greater risk of developing hypertriglyceridemia or having lower HDL-cholesterol. This could be attributed to a lower clearance of both hepatically and intestinally derived triacylglycerol remnants that have been described after high GI meals [49].

Regarding fasting glucose concentrations, there is a great consensus about the beneficial role of low-GI carbohydrate diets on the management of type 2 diabetes. However, the glucose and insulin downregulating role attributed to low-GI or GL diets is still controversial. In a recent meta-analysis of 14 long-term RCT comparing low glycemic index/load versus high glycemic index/load diets, fasting insulin concentrations reduced more in participants following low-GI diets compared with those following high-GI diets, whereas no significant changes were found for fasting glucose and glycosylated hemoglobin [40]. These results are in line with those of a recent 6-month RCT conducted by our group in which participants in the low-GI/low-GL group had significantly greater reductions in fasting plasma insulin, HOMA and HOMA-beta cell than participants in the high-GI/high-GL. However, no significant changes in fasting plasma glucose were observed between

intervention groups at the end of follow-up [42]. Accordingly, in the present analysis, we failed to find any significant relationhip between GI or GL and the component of the MetS related to glucose concentrations.

This study does have several limitations that need to be taken into account. First, it was conducted in adult subjects who are at high cardiovascular risk, so the results cannot be generalized to other populations. Second, there may be some dietary measurement error. The FFQ used to collect the dietary data was not designed to assess dietary GI and dietary GL. However, after validation, we concluded that the GL data collected by the FFQ was more accurate than the GI data. Third, the GI values used to calculate the dietary GI and GL were derived from the glycemic index and glycemic load international tables and may differ from Spanish food values. In order to minimize these differences, for the foods that were not in the tables we calculated the average of similar foods that were. Fourth, we cannot discount a residual effect of intervention diets on the present results. To avoid this potential confounding effect, longitudinal Cox regression models were adjusted for each dietary intervention group. The major strengths of the present study are that it is the first study to evaluate the associations between changes in dietary GI and GL and the risk of MetS and all of its features, conducted in a large cohort of both men and women, using a GI/GL validated food frequency questionnaire.

In conclusion, our results suggest that both dietary GI and GL have a potential role in the development of MetS and some of its features in a cohort of Mediterranean elderly subjects at high cardiovascular risk. Other longitudinal studies analyzing the possible associations between dietary GI or GL and MetS are needed to confirm our findings.

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Table 1. Baseline characteristics of the study participants by tertiles of GI and GL[a]

	Tertiles of GI at baseline				Tertiles of GL at baseline			
	T1 N=2202	T2 N=2210	T3 N=2210	P value	T1 N=2202	T2 N=2210	T3 N=2210	P value
Age (years)	67.4 ± 6.0	67.2 ± 6.3	66.2 ± 6.1	<0.001	67.3 ± 6.1	67.0 ± 6.1	66.6 ± 6.2	0.001
Women, n (%)	1513 (69)	1290 (59)	985 (45)	<0.001	1438 (35)	1312 (60)	1038 (47)	<0.001
BMI (kg/m^2)	30.1 ± 3.9	29.9 ± 3.9	29.8 ± 3.7	0.24	30.1 ± 3.9	29.9 ± 3.7	29.8 ± 3.8	0.007
Waist circumference (cm)	100 ± 10.6	100.2 ± 10.3	101.1 ± 10	0.01	100.4 ±10.7	100.4 ± 10.2	100.6 ± 10.1	0.753
Overweight or obesity, n (%)[c]	1091 (50)	1028 (47)	985 (45)	0.006	1092 (50)	1039 (47)	973 (44)	0.002
Hypertension, n (%)	1801 (82)	1795 (82)	1862 (85)	0.013	1811 (82)	1812 (82)	1835 (83)	0.558
Dyslipidemia, n (%)	1593 (72)	1586 (72)	1611 (73)	0.685	1558 (71)	1600 (72)	1632 (74)	0.043
Type 2 diabetes mellitus, n (%)	1320 (60)	1114 (51)	848 (39)	<0.001	1341 (70)	1077 (49)	864 (39)	<0.001
Medication use, n (%)								
Antihypertensive drugs	1618 (74)	1557 (71)	1629 (74)	0.123	1630 (74)	1602 (73)	1572 (71)	0.126
Hypolipidemic drugs	1128 (51)	1046 (48)	1038 (47)	0.055	1116 (51)	1082 (49)	1014 (46)	0.004
Antidiabetic drugs	916 (42)	768 (35)	539 (25)	<0.001	945 (43)	721 (33)	557 (25)	<0.001
Tobacco use[b]								
Never smoker, n (%)	1537 (70)	1385 (63)	1146 (52)		1456 (66)	1394 (63)	1218 (55)	
Current smoker, n (%)	208 (9)	277 (13)	437 (20)		246 (11)	294 (13)	382 (17)	
Former smoker, n (%)	457 (21)	540 (25)	619 (28)	<0.001	500 (23)	514 (23)	602 (27)	<0.001
Education level, n (%)								
Primary education	1762 (80)	1675 (76)	1651 (75)		1745 (79)	1706 (78)	1637 (74)	
Secondary education	286 (13)	368 (17)	372 (17)		324 (15)	322 (15)	380 (17)	
Academic/graduate	154 (7)	159 (7)	179 (8)	0.001	133 (6)	174 (8)	185 (8)	0.001
Leisure-time physical activity, (MET-min/day)	234.6 ± 235.2	230.6 ±232.2	234.1 ±251.5	0.833	219.9 ± 218.3	230.6 ± 235.7	248.76 ± 262.5	<0.001
Intervention group, n (%)								
MedDiet + EVOO	778 (35)	733 (33)	774 (35)		765 (35)	719 (33)	801 (36)	
MedDiet + Nuts	688 (31)	772 (35)	680 (31)		689 (32)	736 (33)	706 (32)	
Control Diet	736 (33)	697 (32)	748 (34)	0.028	739 (34)	747 (34)	695 (32)	0.102
MedDiet adherence	8.79 ± 1.87	8.74 ± 1.89	8.46 ± 1.96	<0.001	8.61 ± 1.79	8.79 ± 1.92	8.59 ± 2	0.001

[a]Data are given as mean±SD or number (%) unless otherwise indicated.
[b]Current smoker was defined as >1 cigarette or cigar or pipe per day; former smoker was defined as not smoking for ≥ one year.
[c]Overweight was defined as BMI ≥25 kg/m^2 and obesity as BMI ≥30 kg/m^2.
GI: Glycemic index, GL: Glycemic Load, MET: Metabolic Equivalent of Task. MedDiet+EVOO=Mediterranean diet supplemented with Extra Virgin Olive Oil, MedDiet+nuts=Mediterranean diet supplemented with nuts.

Table 2 Baseline dietary characteristics of the study population by tertiles of glycemic index and glycemic load[a]

	Tertiles of GI at baseline				Tertiles of GL at baseline			
	T1	T2	T3	P value	T1	T2	T3	P value
	N=2202	N=2210	N=2210		N=2202	N=2210	N=2210	
Energy intake, kcal/day	2060 ± 492	2253 ± 527	2421 ± 549	<0.001	1787 ± 347	2220 ± 357	2728 ± 441	<0.001
Energy from total carbohydrates, % energy	39,8 ± 6,9	41,5 ± 7,0	43,9 ± 7,0	<0.001	37,0 ± 6,2	41,7 ± 5,8	46,5 ± 6,0	<0.001
Energy from total protein, % energy	17,7 ± 3,0	16,6 ± 2,6	15,6 ± 2,4	<0.001	17,9 ± 3,1	16,5 ± 2,5	15,4 ± 2,2	<0.001
Energy from total fat, % energy	40,8 ± 6,9	39,6 ± 6,7	37,3 ± 6,5	<0.001	42,9 ± 6,5	39,3 ± 6,1	35,5 ± 5,8	<0.001
SFA intake, % energy	1,2 ± 0,3	1,1 ± 0,2	1,0 ± 0,2	<0.001	1,2 ± 0,2	1,1 ± 0,2	1,0 ± 0,2	<0.001
MUFA intake, % energy	2,2 ± 0,5	2,2 ± 0,5	2,1 ± 0,5	<0.001	2,4 ± 0,5	2,2 ± 0,5	1,9 ± 0,4	<0.001
PUFA intake, % energy	0,7 ± 0,2	0,7 ± 0,2	0,7 ± 0,2	<0.001	0,7 ± 0,2	0,7 ± 0,2	0,6 ± 0,2	<0.001
Alcohol intake, g/1,000 kcal	2,4 ± 4,5	3,3 ± 5,1	4,6 ± 6,4	<0.001	3,2 ± 5,6	3,4 ± 5,5	3,7 ± 5,3	0.022
Fiber intake, g/1,000 kcal	12,4 ± 3,5	11,6 ± 3,3	10,4 ± 3,2	<0.001	11,7 ± 3,4	11,5 ± 3,4	11,3 ± 3,5	<0.001
Fruit intake, g/1,000 kcal	178,9 ± 81,9	154,0 ± 70,2	134,1 ± 61,8	<0.001	180,5 ± 82,8	154,5 ± 68,9	132,0 ± 60,6	<0.001
Vegetable intake, g/1,000 kcal	204,3 ± 101,3	172,7 ± 85,7	129,4 ± 70,3	<0.001	176,3 ± 92,1	168,9 ± 93,2	161,2 ± 90,0	<0.001
Cereal intake, g/1,000 kcal	10,5 ± 7,2	9,4 ± 5,3	8,6 ± 5,5	<0.001	10,6 ± 7,2	9,5 ± 5,7	8,4 ± 4,9	<0.001
Legumes intake, g/1,000 kcal	79,3 ± 28,3	100,2 ± 30,0	121,4 ± 36,6	<0.001	83,0 ± 30,3	101,5 ± 34,0	116,4 ± 35,9	<0.001
Dairy product intake, g/1,000 kcal	237,9 ± 108,8	166,4 ± 84,9	122,1 ± 74,0	<0.001	200,0 ± 113,0	172,2 ± 96,8	154,2 ± 90,2	<0.001
Meat intake, g/1,000 kcal	62,1 ± 26,5	60,4 ± 24,1	56,9 ± 23,1	<0.001	69,4 ± 27,7	58,9 ± 22,3	51,1 ± 19,9	<0.001
Fish intake, g/1,000 kcal	49,4 ± 24,5	46,1 ± 22,6	42,3 ± 20,6	<0.001	53,9 ± 25,5	45,9 ± 21,2	38,0 ± 18,3	<0.001
Olive oil intake, g/1,000 kcal	18,8 ± 8,3	17,9 ± 7,9	17,1 ± 7,4	<0.001	21,2 ± 8,7	17,8 ± 7,2	14,8 ± 6,3	<0.001
Nut intake, g/1,000 kcal	4,8 ± 6,4	4,6 ± 5,5	3,6 ± 4,8	<0.001	4,4 ± 6,3	4,5 ± 5,6	4,1 ± 4,9	0.039
Glycemic index	51.2 ± 2.5	56.4 ± 1.2	62.1 ± 2.6	<0.001	53.3 ± 4.2	56.9 ± 4.3	59.5 ± 4.2	<0.001
Glycemic load	88.1 ± 27.9	110.0 ± 33.8	136.0 ± 41.1	<0.001	71.3 ± 13.4	106.9 ± 9.6	155.9 ± 29.8	<0.001

[a]Data are mean±SD. Abbreviations: GI: Glycemic index, GL: Glycemic load; SFA, saturated fat; MUFA, monounsaturated fat; PUFA, polyunsaturated fat.

Table 3. Odds ratio and 95% of confidence intervals for the association between MetS and baseline, dietary GI or GL in 3324 non-diabetic participants[a]

	GI at baseline					GL at baseline				
	Odds ratio (95% CI)					Odds ratio (95% CI)				
Mean±SD	T1 52.2±2.5	T2 57.5±1.3	T3 63.1±2.6	P for trend	Continuous[e] 57.6±5.0	T1 78.0±14.0	T2 114.3±9.4	T3 63.2±29.6	P for trend	Continuous[e] 118.5±40.1
Metabolic syndrome[b]	**n=1108**	**n=1108**	**n=1108**		**n=3324**	**n=1108**	**n=1108**	**n=1108**		**n=3324**
Unadjusted model	1	1.09 (0.93, 1.29)	1.19 (1.00, 1.40)	0.046	1.11 (1.03, 1.18)	1	0.96 (0.82, 1.14)	1.03 (0.87, 1.21)	0.746	1.01 (1.00, 1.03)
Fully adjusted model[c,d]	1	1.18 (0.98, 1.42)	1.33 (1.09, 1.63)	0.005	1.19 (1.09, 1.29)	1	1.10 (0.89, 1.35)	1.07 (0.79, 1.46)	0.657	1.06 (1.01, 1.11)
Abdominal obesity	**n= 1097**	**n= 1102**	**n= 1103**		**n=3302**	**n=1098**	**n=1098**	**n= 1106**		**n=3302**
Unadjusted model	1	0.80 (0.66, 0.97)	0.73 (0.60, 0.88)	0.001	0.86 (0.79, 0.93)	1	0.65 (0.54, 0.79)	0.60 (0.49, 0.72)	<0.001	0.96 (0.94, 0.98)
Fully adjusted model[c]	1	1.17 (0.90, 1.53)	1.44 (1.08, 1.93)	0.014	1.15 (1.01, 1.30)	1	0.82 (0.60, 1.11)	0.86 (0.56, 1.34)	0.543	1.02 (0.95, 1.09)
Hypertriglyceridemia	**n= 1102**	**n= 1101**	**n= 1104**		**n=3307**	**n= 1099**	**n= 1103**	**n= 1105**		**n=3307**
Unadjusted model	1	1.19 (0.99, 1.43)	1.42 (1.19, 1.71)	<0.001	1.20 (1.11, 1.29)	1	1.17 (0.98, 1.41)	1.37 (1.15, 1.65)	0.001	1.04 (1.02, 1.06)
Fully adjusted model[c]	1	1.12 (0.92, 1.35)	1.24 (1.01, 1.52)	0.043	1.14 (1.05, 1.25)	1	1.19 (0.96, 1.49)	1.27 (0.92, 1.74)	0.148	1.08 (1.03, 1.13)
Low HDL-cholesterol	**n= 1103**	**n= 1104**	**n= 1103**		**n=3310**	**n= 1099**	**n= 1106**	**n= 1105**		**n=3310**
Unadjusted model	1	1.15 (0.95, 1.40)	1.08 (0.89, 1.31)	0.463	1.01 (0.94, 1.10)	1	1.00 (0.82, 1.21)	1.00 (0.82, 1.21)	0.983	1.01 (0.99, 1.03)
Fully adjusted model[c]	1	1.24 (1.01, 1.52)	1.27 (1.02, 1.59)	0.034	1.09 (0.99, 1.20)	1	0.98 (0.78, 1.24)	0.87 (0.62, 1.23)	0.445	1.03 (0.97, 1.09)
High blood pressure	**n= 1108**	**n= 1108**	**n= 1107**		**n=3323**	**n= 1108**	**n= 1107**	**n= 1108**		**n=3323**
Unadjusted model	1	1.33 (0.92, 1.92)	1.25 (0.87, 1.80)	0.222	1.06 (0.91, 1.24)	1	0.91 (0.63, 1.33)	0.96 (0.66, 1.40)	0.863	0.99 (0.96, 1.03)
Fully adjusted model[c]	1	1.47 (0.99, 2.18)	1.55 (1.01, 2.39)	0.044	1.17 (0.97, 1.40)	1	1.09 (0.69, 1.72)	1.27 (0.65, 2.49)	0.482	1.02 (0.92, 1.13)
High fasting glucose	**n=1070**	**n=1075**	**n=1071**		**n=3216**	**n=1066**	**n=1072**	**n=1078**		**n=3216**
Unadjusted model	1	0.87 (0.73, 1.04)	1.01 (0.85, 1.20)	0.930	1.04 (0.97, 1.12)	1	1.05 (0.88, 1.25)	0.99 (0.83, 1.18)	0.924	1.00 (0.99, 1.02)
Fully adjusted model[c]	1	0.84 (0.70, 1.01)	0.91 (0.75, 1.12)	0.376	1.01 (0.92, 1.09)	1	1.05 (0.85, 1.30)	0.87 (0.64, 1.20)	0.402	0.99 (0.95, 1.04)

[a] Values are expressed as Odds ratio and 95% Confidence intervals. Logistic regression models were used to assess the prevalence of Metabolic Syndrome according to tertiles of glycemic index and glycemic load.

[b] Participants were considered to have MetS if they had three or more of the following features: a) abdominal obesity for European individuals (≥88 cm and ≥102cm in women and men, respectively), b) hypertriglyceridemia [≥150 g/dL] or drug treatment for elevated TG, c) low concentrations of HDL-cholesterol [<40 mg/dL in men; <50 mg/dL in women] or drug treatment for low HDL-cholesterol, d) high blood pressure (systolic ≥130 and/or diastolic ≥85 mmHg) or antihypertensive drug treatment, e) high fasting glucose [≥100 mg/dL] or drug treatment for diabetes.

[c] The fully adjusted model was adjusted for sex, age, BMI at baseline, recruiting center, tobacco use (never smoker, current smoker, former smoker), education (primary education, secondary education, graduate/academic) leisure-time physical activity (MET-min/d), Mediterranean diet score, total energy intake (kcal/d), alcohol intake (continuous, adding a quadratic term) and quintiles of dietary fiber, total fat and protein intakes.

[d] Statistical models with MetS as outcome were also adjusted for all MetS features at baseline.

[e] Continuous variables are expressed as 5 point-increases in GI and 10 point-increases in GL.

Abbreviations: GI: Glycemic index, GL: Glycemic load and MetS: Metabolic syndrome

Table 4. Odds ratio and 95% confidence intervals for the association between MetS and baseline dietary GI or GL in 3282 diabetic participants[a]

	GI at baseline					GL at baseline				
	Odds ratio (95% CI)					Odds ratio (95% CI)				
	T1	T2	T3	P for	Continuous[e]	T1	T2	T3	P for	Continuous[e]
Mean±SD	50.5±2.5	55.4±1.2	60.8±2.6	trend	55.6±4.7	66.3±12.7	99.3±9.5	147.2±29.5	trend	104.2±38.4
Metabolic syndrome[b]	**n=1094**	**n=1094**	**n=1094**		**n=3282**	**n=1094**	**n=1094**	**n=1094**		**n=3282**
Unadjusted model	1	0.90 (0.73, 1.11)	0.86 (0.70, 1.06)	0.166	0.95 (0.87, 1.04)	1	1.00 (0.80, 1.24)	0.73 (0.59, 0.90)	0.002	0.96 (0.94, 0.99)
Fully adjusted model[c,d]	1	1.01 (0.78, 1.30)	1.13 (0.86, 1.50)	0.354	1.08 (0.95, 1.22)	1	1.15 (0.86, 1.55)	0.96 (0.64, 1.46)	0.803	1.01 (0.95, 1.08)
Abdominal obesity	**n= 1085**	**n= 1083**	**n= 1077**		**n=3245**	**n= 1081**	**n= 1077**	**n= 1087**		**n=3245**
Unadjusted model	1	0.84 (0.69, 1.02)	0.66 (0.54, 0.80)	<0.001	0.85 (0.78, 0.93)	1	0.94 (0.77, 1.15)	0.69 (0.57, 0.83)	<0.001	0.96 (0.94, 0.97)
Fully adjusted model[c]	1	0.96 (0.72, 1.28)	0.88 (0.65, 1.19)	0.398	0.99 (0.86, 1.13)	1	1.00 (0.72, 1.37)	0.90 (0.58, 1.42)	0.646	1.01 (0.95, 1.09)
Hypertriglyceridemia	**n= 1049**	**n= 1061**	**n= 1062**		**n=3172**	**n= 1047**	**n= 1054**	**n= 1071**		**n=3172**
Unadjusted model	1	1.08 (0.90, 1.28)	1.04 (0.87, 1.24)	0.730	1.02 (0.95, 1.11)	1	0.95 (0.79, 1.13)	0.89 (0.74, 1.06)	0.195	0.99 (0.97, 1.01)
Fully adjusted model[c]	1	1.06 (0.88, 1.28)	1.00 (0.82, 1.23)	0.990	1.01 (0.92, 1.10)	1	1.00 (0.80, 1.24)	0.93 (0.68, 1.27)	0.641	0.99 (0.94, 1.04)
Low HDL-cholesterol	**n= 1049**	**n= 1056**	**n= 1055**		**n=3160**	**n= 1042**	**n= 1052**	**n= 1066**		**n=3160**
Unadjusted model	1	1.14 (0.96, 1.37)	1.01 (0.85, 1.21)	0.954	1.01 (0.93, 1.09)	1	0.85 (0.71, 1.02)	0.89 (0.74, 1.06)	0.207	0.99 (0.97, 1.01)
Fully adjusted model[c]	1	1.18 (0.97, 1.42)	1.09 (0.89, 1.35)	0.424	1.04 (0.95, 1.14)	1	0.91 (0.73, 1.14)	1.00 (0.73, 1.37)	0.990	1.01 (0.96, 1.06)
High blood pressure	**n= 1094**	**n= 1094**	**n= 1093**		**n=3281**	**n= 1094**	**n= 1094**	**n= 1093**		**n=3281**
Unadjusted model	1	0.71 (0.51, 0.99)	1.09 (0.76, 1.57)	0.583	1.07 (0.92, 1.24)	1	1.05 (0.74, 1.49)	0.83 (0.59, 1.16)	0.232	0.97 (0.94, 1.01)
Fully adjusted model[c]	1	0.74 (0.52, 1.06)	1.27 (0.84, 1.92)	0.197	1.16 (0.97, 1.38)	1	1.16 (0.76, 1.77)	1.37 (0.76, 2.46)	0.294	1.07 (0.98, 1.17)

[a] Values are expressed as Odds ratio and 95% Confidence intervals. Logistic regression models were used to assess the prevalence of metabolic syndrome according to tertiles of glycemic index and glycemic load.

[b] Participants were considered to have MetS if they had three or more of the following features: a) abdominal obesity for European individuals (≥88 cm and ≥102cm in women and men, respectively), b) hypertriglyceridemia [≥150 g/dL] or drug treatment for elevated TG, c) low concentrations of HDL-cholesterol [<40 mg/dL in men; <50 mg/dL in women] or drug treatment for low HDL-cholesterol, d) high blood pressure (systolic ≥130 and/or diastolic ≥85 mmHg) or antihypertensive drug treatment.

[c] The fully adjusted model was adjusted for sex,, age, BMI at baseline, recruiting center, tobacco use (never smoker, current smoker, former smoker), education (primary education, secondary education, graduate/academic) leisure-time physical activity (MET-min/d), Mediterranean diet score, total energy intake (kcal/d), alcohol intake (continuous, adding a quadratic term) and quintiles of dietary fiber, total fat and protein intakes.

[d] Statistical models with MetS as outcome were also adjusted for all MetS features at baseline.

[e] Continuous variables are expressed as 5 points-increase of GI and 10 points-increase of GL.

Abbreviations: GI: Glycemic index, GL: Glycemic load and MetS: Metabolic syndrome.

Table 5. HR for incident cases of MetS and its features according to changes in dietary GI or GL during the follow-up[a]

	Changes of GI					Change of GL				
	Hazard ratio (95% CI)					Hazard ratio (95% CI)				
	T1	T2	T3	P for	Continuous[c]	T1	T2	T3	P for	Continuous[c]
Mean±SD	-4.1±2.7	-0.1±1.4	3.9±2.6	trend	-0.2±4.0	-45.0±25.6	-2.1±7.8	33.9±19.9	trend	-3.7±37.5
Metabolic syndrome[b]	**n=610**	**n=611**	**n=611**		**n=1832**	**n=610**	**n=611**	**n=611**		**n=1832**
Cases	302	307	322		931	301	303	327		931
Unadjusted model	1	1.01 (0.86, 1.19)	1.15 (0.98, 1.34)	0.089	1.07 (0.99, 1.17)	1	1.06 (0.90, 1.24)	1.11 (0.95, 1.30)	0.197	1.10 (1.02, 1.19)
Fully adjusted model[c,d]	1	1.05 (0.89, 1.24)	1.19 (1.01, 1.40)	0.050	1.10 (1.01, 1.19)	1	1.18 (0.99, 1.40)	1.23 (1.03, 1.48)	0.070	1.11 (1.03, 1.20)
Abdominal obesity	**n= 550**	**n= 550**	**n= 550**		**n=1563**	**n= 521**	**n= 521**	**n= 521**		**n=1563**
Cases	220	232	252		704	219	233	252		704
Unadjusted model	1	1.05 (0.87, 1.26)	1.22 (1.02, 1.46)	0.029	1.02 (0.93, 1.12)	1	1.10 (0.91, 1.32)	1.20 (1.00, 1.44)	0.048	1.02 (0.99, 1.04)
Fully adjusted model[c]	1	1.07 (0.88, 1.30)	1.19 (0.98, 1.44)	0.079	1.04 (0.94, 1.14)	1	1.15 (0.93, 1.43)	1.38 (1.09, 1.75)	0.008	1.05 (1.02, 1.07)
Hypertriglyceridemia	**n= 1093**	**n= 1093**	**n= 1093**		**n=3279**	**n= 1093**	**n= 1093**	**n= 1093**		**n=3279**
Cases	301	269	330		900	294	285	321		900
Unadjusted model	1	0.90 (0.76, 1.06)	1.18 (1.01, 1.38)	0.043	1.02 (0.93, 1.12)	1	0.98 (0.83, 1.15)	1.10 (0.94, 1.28)	0.262	1.09 (0.99, 1.04)
Fullyadjusted model[c]	1	0.90 (0.76, 1.07)	1.15 (0.97, 1.36)	0.111	1.04 (0.94, 1.14)	1	1.04 (0.86, 1.26)	1.22 (0.98, 1.51)	0.062	1.04 (1.01, 1.07)
Low HDL-cholesterol	**n= 1164**	**n= 1165**	**n= 1165**		**n=3494**	**n= 1164**	**n= 1165**	**n= 1165**		**n=3494**
Cases	368	344	382		1094	358	348	388		1094
Unadjusted model	1	0.96 (0.83, 1.11)	1.15 (1.00, 1.33)	0.059	1.02 (1.00, 1.05)	1	0.97 (0.84, 1.13)	1.08 (0.93, 1.24)	0.323	1.02 (1.00, 1.05)
Fully adjusted model[c]	1	1.04 (0.89, 1.21)	1.23 (1.06, 1.44)	0.008	1.05 (1.02, 1.09)	1	1.15 (0.97, 1.36)	1.36 (1.12, 1.63)	0.001	1.04 (1.01, 1.08)
High blood pressure	**n= 112**	**n= 113**	**n= 112**		**n=337**	**n= 112**	**n= 113**	**n= 112**		**n=337**
Cases	90	97	98		285	89	95	101		285
Unadjusted model	1	1.27 (0.95, 1.70)	1.37 (1.03, 1.83)	0.031	1.08 (1.00, 1.17)	1	1.22 (0.91, 1.63)	1.49 (1.12, 1.98)	0.007	1.03 (0.94, 1.13)
Fully adjusted model[c]	1	1.38 (0.99, 1.91)	1.48 (1.04, 2.10)	0.027	1.11 (1.01, 1.21)	1	1.38 (0.97, 1.97)	1.51 (0.99, 2.28)	0.051	1.01 (0.92, 1.10)
High fasting glucose	**n= 576**	**n= 576**	**n= 576**		**n=1728**	**n= 576**	**n= 576**	**n= 576**		**n=1728**
Cases	250	245	279		774	260	253	261		774
Unadjusted model	1	0.92 (0.77, 1.10)	1.14 (0.96, 1.36)	0.118	1.03 (0.94, 1.13)	1	0.96 (0.81, 1.14)	0.89 (0.75, 1.06)	0.201	0.99 (0.97, 1.01)
Fully adjusted model[c]	1	0.91 (0.76, 1.10)	1.11 (0.92, 1.33)	0.246	1.04 (0.92, 1.10)	1	1.01 (0.83, 1.23)	0.93 (0.74, 1.16)	0.483	0.98 (0.96, 1.01)

[a] Only participants without metabolic syndrome at baseline were included in the analysis. Values are expressed as Hazard ratio and 95% Confidence intervals. Cox regression models were used to assess the prevalence of Metabolic syndrome according to tertiles of glycemic index and glycemic load.

[b] Participants were considered to have MetS if they had three or more of the following features: a) abdominal obesity for European individuals (≥88 cm and ≥102cm in women and men, respectively), b) hypertriglyceridemia [≥150 g/dL] or drug treatment for elevated TG, c) low concentrations of HDL-cholesterol [<40 mg/dL in men; <50 mg/dL in women] or drug treatment for low HDL-cholesterol, d) high blood pressure (systolic ≥130 and/or diastolic ≥85 mmHg) or antihypertensive drug treatment, e) high fasting glucose [≥100 mg/dL] or drug treatment for diabetes.

[c] The fully adjusted model was adjusted for sex,, age, BMI at baseline, recruiting center, intervention group, tobacco use (never smoker, current smoker, former smoker), education (primary education, secondary education, graduate/academic) leisure-time physical activity (MET-min/d), Mediterranean diet score, total energy intake (kcal/d), alcohol intake (continuous, adding a quadratic term) and quintiles of dietary fiber, total fat and protein intakes.

[d] Statistical models with MetS as outcome were also adjusted for all MetS features at baseline.
[c] Continuous variables are expressed as 5 point-increases in GI and 10 point-increases in GL.
Abbreviations: GI: Glycemic index, GL: Glycemic load and MetS: Metabolic syndrome.

VIII. DISCUSSION

The research undertaken for this thesis aimed to investigate the possible role of the GI on reducing risk of chronic diseases, focusing on the development of MetS and its features and the effects of GI on weight loss and its potential mechanisms, especially chronic inflammation. The potential role of GI or GL in the development of MetS and its features was investigated in the PREDMIED study, a cohort of Mediterranean subjects at high CVD risk. The relationship between GI/GL and markers of inflammation were also assessed in a prospective epidemiologic study carried out in the PREDIMED cohort. Finally, the effects of GI and GL on weight loss have been evaluated in a 6-month randomized controlled trial where the participants were allocated in one of the three intervention energy-restricted diets. Additionally in the same RCT, potential mechanisms linking GI and weight loss were also evaluated, especially effects on systemic inflammation and satiety. The findings presented in the current thesis contribute to extent the knowledge of the beneficial effects of GI and GL in the management and development of some chronic diseases.

8.1 Associations between dietary GI or GL and metabolic syndrome

In the current prospective analysis conducted in the PREDIMED cohort, we have shown for the first time that an increase in dietary GI and GL during the follow-up was associated with a reduced risk of MetS development and also some of some of its features, including hypertriglyceridemia, abdominal obesity and lower HDL-cholesterol components of the MetS. This results support previous evidence linking the intake of high-GI or high-GL foods with a higher risk of CVD risk factors such as MetS.

Current scientific evidence linking dietary GI and GL and disease risk is large and non-conclusive. Few studies have evaluated the cross-sectional associations between overall dietary GI or GL and MetS (295,310,312,316) with inconsistent results. Whereas two of them found a significant positive association between GI or GL and MetS prevalence (295,312), the other two reported no

significant associations (310,316). Our results showed a significant positive association between GI and GL, and prevalence of MetS among non-diabetic participants. However, we have also observed, for the first time, a direct relationship between changes in GI and GL and an increased risk of MetS incidence, suggesting a causal relationship between carbohydrate quality and MetS development.

Abdominal obesity is one of the main features of the MetS and has been identified as an independent risk factor for several chronic conditions such as T2DM, CVD and cancer. GI has been investigated as a preventive nutritional strategy or treatment of body weight management and fat distribution. To date, contradictory results have been published regarding the possible beneficial effect of GI on weight loss. Whereas a significant weight-loss related to low-GI diets was observed in short-term clinical trials (322), no beneficial effects were observed in the long term (390), and these diets have not been included in the nutritional recommendations of the European Food Safety Authority in the context of obesity treatment (391). Contradictory results have also been reported regarding abdominal obesity. Within the observational studies analyzing the associations between GI/GL and abdominal obesity, few of them found non-significant results (310,316), whereas others found a positive relationship (311,312,315). The results of a huge observational study conducted in 89,432 participants from 5 different European countries showed a significant increase of 0.26 cm of waist circumference per year for a 10-unit increase in GI (311). Additionally, a recent meta-analysis of randomized clinical trials with a follow-up of at least 6 month reported no significant effect of GI/GL on waist circumference (390). In the present study, non-diabetic participants in the highest GI tertile showed a large waist girth, thus contributing to the higher prevalence of MetS observed. Accordingly, in the longitudinal assessment the higher risk of developing abdominal obesity observed in those participants who increased their GL during the follow-up reinforces the potentially negative effect of these diets on such an important metabolic cardiovascular factor as abdominal obesity.

In agreement with previous findings (392–394), we also found a significant association between the highest GI tertile and blood pressure in non-diabetic subjects. Moreover, we found that the

risk of developing hypertension increased with the increase in GI during the follow-up and a trend with increased GL at the limit of statistical significance. These longitudinal results support those published by Philippou et al. who reported significantly higher reductions in 24-h blood pressure after a 6-month low GI diet in comparison to a high-GI diet (394). This may be because increased insulin resistance, plasma cholesterol and abdominal obesity, all features of the MetS, act directly on the arterial wall (395) and as potential mediators of sodium retention and volume expansion thus increasing both blood pressure (166,167) and inflammation, and affecting the oxide nitric system (396).

High dietary GI or GL have also been associated with lower concentrations of HDL-cholesterol and increased levels of tryglycerides (397–399). In a cross-sectional study of more than 18,000 non-diabetic middle-aged and older women, those in the highest quintiles of both GI and GL showed lower HDL-cholesterol levels and significantly higher TG concentrations (399). Frost et al., also reported similar results in a cohort of British subjects (398). However, in a recent meta-analysis of randomized clinical trials with at least a 6-month follow-up, GI/GL were not observed to have a significant effect on HDL-cholesterol levels (390). In our study, we also found a positive association between GI or GL and low HDL-cholesterol and hypertriglyceridemia in non-diabetic subjects. Moreover, subjects who increased their dietary GI or GL during the follow-up also showed a greater risk of developing hypertriglyceridemia or having lower HDL-cholesterol. This could be attributed to a lower clearance of both liver and intestinally derived triacylglycerol remnants described after high GI meals (400).

Regarding fasting glucose levels, there is a great consensus about the beneficial role of low-GI carbohydrate diets on the management of type 2 diabetes. However, the glucose and insulin downregulating role attributed to low-GI or GL diets is still controversial. In a recent meta-analysis of 14 long-term RCT comparing low GI/GL versus high GI/GL diets, fasting insulin concentrations reduced more in participants following low-GI diets, whereas no significant changes were found for fasting glucose and glycosilated hemoglobin (390). Accordingly, in the

present analysis, we failed to find any significant association between GI or GL and the component of the MetS related to glucose levels.

8.2 Associations between GI and GL, and chronic inflammation.

The results of the cross-sectional analysis conducted in 511 elderly subjects show an inverse association between plasma leptin and adiponectin concentrations, and dietary GI and GL. Furthermore, in a prospective longitudinal assessment after a 1-year follow-up we demonstrated an inverse association between an increased dietary GI or GL and changes in both plasma leptin and adiponectin levels, independently of potential dietary and non-dietary confounders. However, no significant relationships were observed between dietary GI or GL and other adipokine metabolic markers analyzed.

It is quite clear that energy homeostasis requires a fine regulation of food intake, nutrient absorption, energy expenditure and storage. These processes are coordinated by the central nervous system after controlling the homeostatic signals derived from peripheral tissues. Since leptin discovered, the secretory activities of adipose tissue have increased exponentially with more than 50 adipocyte-derived products that make different contributions to obesity and its pathophysiological features (401). Therefore, because a low grade of chronic inflammation is now recognized as one of the central mechanisms underlying obesity and associated comorbidities, the potential effect of dietary GI and GL on inflammatory modulation seems relevant. However, the few studies carried out to date are controversial because they focus on the plasma C-reactive protein and do not evaluate the long-term effects of GI or GL on adipostats or other adipokines related to obesity and comorbidities (364,402).

The results of our 1-year prospective longitudinal study conducted in a large sample of subjects at high cardiovascular risk are in agreement with the adipostatic theory. The adipokines, leptin and adiponectin, are considered to be the two major adipostats in humans because of their role in the central nervous system and in peripheral tissues (403,404). In our study, we have demonstrated that an increase in the dietary GI and GL are associated with a decrease in leptin

and adiponectin plasma concentrations. Our results are in agreement with those obtained using an intervention study conducted in rats fed with a high-GI starch diet for 12 weeks (405) and those reported in a postprandial state (406). Therefore, if we consider that higher leptin levels are associated with a decrease in food intake and an increase in energy expenditure acting at the hypothalamic central level (407), the down-regulation of leptin induced by an increase in GI or GL observed in our study could be considered as a mechanism favoring the weight gain and obesity attributed to high-GI diets. Moreover, because leptin also exerts autocrine or paracrine actions increasing lipolysis and decreasing lipogenesis, the decrease in circulating plasma leptin levels observed in our study may lead to a decrease in fatty-acid oxidation and an increase in glucose oxidation, which favors fat deposition. Finally, because leptin is primarily known as a satiety factor, the decrease in plasma leptin after a high-GI diet sustained the concept that these diets are less satiating than low-GI diets (408).

Adiponectin is the most abundant adipocytokine in humans. A low level of circulating adiponectin results in insulin resistance, glucose intolerance, dyslipidemia and atherosclerosis (409). Recently, adiponectin has been identified in the cerebrospinal fluid of rodents suggesting that it has an important role in the central regulation of energy intake and energy expenditure (410). However, although the central effects of adiponectin on energy balance are still unclear and controversial in humans (404) the results of our study support the hypothesis that high-GI-induced hypoadiponectinemia could be to the detriment of obesity. Moreover, the hypoadiponectinemia induced by the increase in dietary GI that we observed and reported in a previous epidemiologic study (411) could partly explain the relationship between the GI of the diet and the increased risk of T2DM and CVD associated with the consumption of this type of diet.

In our study, we failed to show that the GI and GL had any relationship with incretins, other adipokines or related molecules. We only observed significantly higher levels of TNF and a trend to higher levels of IL-6 in those subjects in the higher GI quartiles, after adjusting for confounders, suggesting that pro-inflammatory cytokines worsened in those subjects consuming high-GI foods. In a longitudinal manner, we also reported a positive relationship between an

increase in GL and an increase in GIP, but not GLP-1, thus suggesting that a high dietary GL contributes to fat deposition and obesity.

8.3. Effect of GI or GL on weight loss

To our knowledge, this is the first study to simultaneously evaluate the effectiveness of moderate-carbohydrate LGI, moderate-carbohydrate HGI, and LF diets with weight loss as the main outcome. The results presented in the present thesis showed that a LGI diet reduced weight more effectively than did a traditional LF diet, with a HGI.

To date, nearly thirty studies have evaluated the effects of GI or GL on weight management with inconsistent results (323–327,412). A meta-analysis with 6 of the previously mentioned RCT found a beneficial effect of LGI diets. With a total of 202 participants and a duration between 5 weeks and 6 months, the results of the combined RCT showed that participants randomized in the LGI interventions lost -1.1 kg (95%CI -2.0 to -0.2) more than those allocated in the HGI group (413). However, the RCTs used in the meta-analysis did not adjust intervention for potential dietary confounders such as protein or total fiber. However these results are not supported by those published in an another meta-analysis conducted by Schwingshackl et al. Including 15 long-term (between 12 to 24 months) RCTs, the results of this meta-analysis showed no beneficial effects of the LGI diets on body weight or waist circumference in comparison with the HGI diets (390). The results from our RCT showed that those participants in the LGI or HGI lost more weight than those in the traditional LGI diet, although significant differences were only found between LGI and LF groups. These results suggest that diets rich in vegetable fat, mainly extra-virgin olive oil, and moderate amounts of carbohydrates have a greater effect on obesity management than traditional LF diets. Although we didn't observed a significant effect of the GI, significant differences in weight loss were observed between those diets with larger differences in GL, indicating that maybe is the combination of quality and quantity of carbohydrates a key point in the management of obesity. These results are not supported by those showed in the publication nº 2 where those non-diabetic subjects with higher dietary GI were more likely to have abdominal obesity and also with those participants with higher increases in dietary GL during the follow-up

that had a 38% more risk of large waist circumference. This discrepancies observed between the two studies can be explained by the differences in the design of the studies and also by differences between populations.

In the present study no differences were observed between diets in satiety or hunger rates derived from VASs, suggesting that the effect on body weight of low- or high-GI diets is mediated by other mechanisms rather than short-term satiety modulation. Despite this, and in line with the results of short-term satiety studies (346), we observed a non-significant tendency to higher satiety rates and lower hunger rates in the LGI group than in the other groups. With the results of observed in the publication nº 3, where changes in dietary GI and GL were associated with changes in leptin concentrations, we speculated that maybe this relationship could partly explain the observed beneficial effects of low-GI foods on satiety. However, these results do not support those observed from the VASs.

Insulin sensitivity has been thought to have an important association with the effectiveness of GI on weight change (414). However, the reports on the effect of dietary GI/GL on glucose and insulin metabolism provide inconsistent data. The results of a recent systematic review and meta-analysis of RTCs showed no significant effects of diets with different GI or GL on fasting glucose and HbA1c. However, the same meta-analysis showed that LGI diets had a significantly greater effect on fasting insulin than HGI diets (390). In the GLYNDIET study, both insulin sensitivity and resistance significantly improved in participants in the LGI group even after adjusting by changes in body weight, suggesting additional mechanisms linking GI/GL and insulin metabolism rather than body weight reduction. Improvements in glycemia and insulinemia attributable to LGI diets could be mediated by changes in the incretin axis. In this regard, a 28-day weight-maintaining high-GL controlled diet led to significantly lower post-prandial concentrations of GLP-1 than a low-GL diet after a test breakfast (415). The results of our study support a long-term effect of GI on the incretin axis. However, the significant decrease in GIP-1 circulating levels observed in the HGI group cannot explain the higher decrease of glucose levels observed in the same dietary intervention group. The results observed in the PREDIMED cohort are not in line with those

observed in the GLYNDIET study, probably because of differences in the design, methodology and population studied. Further research is needed to understand the exact long-term effect of GI/GL on incretin axis and its implication in obesity and T2DM. Due to the postulated effect of both osteocalcin and uncarboxylated osteocalcin forms on insulin resistance (416), the slightly higher increase in osteocalcin and uncarboxylated osteocalcin in the LGI diet group than in the HGI or LF diet groups observed in our study reinforces the beneficial role that this type of diet plays in insulin metabolism. Overall, our results are in line with those of a previous meta-analysis (414) and support findings from prospective cohort studies that consistently indicate that consumption of lower GI are associated with a lower T2DM risk (294).

As expected, we observed that HDL-cholesterol tended to increase and triglycerides slightly decrease, although the differences observed between groups were non-significant. These results are in line with those observed in the publication nº 2 where changes in dietary GI and GL were associated with an increased risk of low-HDL-cholesterol and hypertriglyceridemia. Although no significant differences were observed between groups in the GLYNDIET study, the results presented here add more evidence to the current knowledge of the beneficial effects of GI on lipid profile and CVD risk factors.

As commented before, inflammatory modulation has also been postulated as a potential mechanism linking dietary GI/GL with the management of obesity and its related comorbidities. Few clinical trials have evaluated the effect of GI/GL on inflammatory markers and most of those that have only focus on the CRP (369,371,372,383,417). In 773 obese adults from the DIOGENES trial, changes in CRP were significantly greater in the LGI than the HGI groups (372). Decreased IL-6, TNFα, PAI-1 and leptin concentrations have also been observed after weight loss induced by LF or LGI hypocaloric diets with no between-group differences (418). Our results from the PREDIMED study also indicate a positive associations between GI and GL and some inflammatory markers such leptin or adiponectin. However, in the GLYNDIET study, subjects allocated to the LGI group show a significant reduction in peripheral CRP and leptin concentrations, and a tendency to a higher decrease in IL-6 after the intervention. However, the changes were shown

to be different between intervention groups. In our study, the GI/GL of the diet was not observed to have any effect on the other inflammatory markers analyzed although, as expected, most of them tend to improve because of the weight loss in all the intervention groups.

8.4 Strengths and Limitations

The major strengths of the current thesis are:

The results from the PREDIMED study were analyzed in a cross-sectional and longitudinal manner in a large cohort of individuals, indicating both association and cause-relationship.

The strengths of the GLYNDIET study are its medium-term duration, the randomized design balanced in each intervention group for sex, age and use of T2DM drugs, and the differences between diets in relation to the GI and GL. Moreover, our study is the first to simultaneously analyze the effect of an LGI, an HGI and an LF diet on weight loss, satiety, glucose and insulin metabolism and several associated metabolic risk markers.

However we recognize that this thesis does have several limitations that need to be taken into account.

First, the results analyzed in the PREDIMED cohort were conducted in adult population who are at high cardiovascular risk. Thus, baseline concentrations of metabolic markers used in this thesis were higher than general population and more prone to be modulated by the dietary intervention. Because of that, the results cannot be generalized to other populations.

Second, there may be some dietary measurement error. The FFQ used to collect the dietary data was not designed to assess dietary GI and dietary GL. However, after validation, we concluded that the GL data collected by the FFQ was more accurate than the GI data. Moreover, due to scarcity of data, it was necessary to use GI values derived from studies conducted in different

countries where the food or its properties may differ from that consumed in Spain. Nevertheless, these limitations would also apply to some other epidemiologic studies and clinical trials involving GI and GL measurements.

Third, the results analyzed in the PREDIMED study were conducted in a cohort that was undergoing nutritional interventions and we cannot discount a residual effect of intervention diets on the present results. However, to address this limitation and to minimize the effect, we have adjusted all longitudinal analyses for the intervention group.

Finaly, in the GLYNDIET study, we used dietary food records during the follow up as an indirect marker of dietary compliance. Lack of specific biochemical markers of dietary compliance related to GI/GL is also a limitation of the study.

IX. CONCLUSIONS

To analyze the association between dietary GI and GL and the risk of to develop MetS and its features in a high cardiovascular risk population.

Our results suggest that both dietary GI and GL have a potential role in the development of MetS and some of its components in a cohort of Mediterranean subjects at high cardiovascular risk.

To analyze the relationship between dietary GI and GL, peripheral adipokines and inflammatory markers in a high cardiovascular risk population.

The consumption of diets with high-GI foods or high dietary GL may modulate plasma concentrations of some cardiometabolic markers thus contributing to weight gain and cardiovascular disease.

To analyze the effectiveness of a high GI/GL diet versus a low-GI/GL and a low-fat diet in body weight loss and the improvement of metabolic profile, through the modulation of some mechanisms related to satiety, inflammation and other metabolic risk markers.

A moderate-CH low-GI diet may be more effective for weight loss than a moderate-CH high-GI diet or a conventional low-fat diet. The metabolic benefits observed for insulin resistance and sensitivity in those subjects following a low-GI diet, and the tendency to improve other inflammatory and associated metabolic risk markers, also indicate that low-GI diets are better tools for managing obesity and its associated comorbidities.

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APPENDIX 1.

GENERAL MEDICAL QUESTIONNAIRE

ESTUDIO PREDIMED

Cuestionario general

Identificador del participante: Nodo | C.Salud | Médico | Paciente | Visita

Nodo: anotar el número de nodo correspondiente.
01. Andalucía - Málaga / 02. Andalucía - Sevilla - S.Pablo / 03. Andalucía - Sevilla - V.Rocío / 04. Baleares / 05. Cataluña - Barcelona norte / 06. Cataluña - Barcelona Sur / 07. Cataluña - Reus - Tarragona / 08. Madrid Norte / 09. Madrid Sur / 10. Navarra / 11. País Vasco / 12. Valencia

C.Salud: anotar el número del centro de salud correspondiente.

Médico: anotar el número del médico correspondiente.

Paciente: anotar el número del paciente correspondiente.

Visita: anotar el número de visita correspondiente.

00. Inclusión - exclusión / 01. Visita Inicial / 02. Visita 3 meses / 03. Visita 1 año / 04. Visita 2 años / 05. Visita 3años

Información de contacto (Pariente o amigo):

Primer apellido | Segundo apellido | Nombre

Teléfono | Teléfono

GRUPO asignado: ◯ Aceite de oliva virgen ◯ Frutos secos ◯ Control

VARIABLES SOCIO DEMOGRÁFICAS

Lugar de nacimiento:

◯ Galicia ◯ La Rioja ◯ Murcia ◯ Castilla la Mancha
◯ Asturias ◯ Aragón ◯ Madrid ◯ Andalucía
◯ Cantabria ◯ Cataluña ◯ Castilla-León ◯ Canarias
◯ País Vasco ◯ Comunidad Valenciana ◯ Extremadura ◯ Baleares
◯ Navarra

País (solo rellenar en caso de extranjeros):

Estado Civil: ◯ Soltero/a ◯ Casado/a ◯ Viudo/a ◯ Divorciado/a ◯ Separado/a ◯ Religioso

¿Cúal es el nivel más alto de escolarización que ha completado?

◯ Titulado Superior o similares ◯ Técnico Escuela Universitaria ◯ Escuela secundaria o Bachiller ◯ Escuela primaria
◯ No sabe leer ni escribir ◯ Datos insuficientes

Número de personas con las que comparte el hogar:

¿Cúal es su situación laboral actual?

◯ Está trabajando ◯ Incapacidad permanente ◯ Ama de casa ◯ Estudiante ◯ Jubilado
◯ Trabaja pero tiene una baja laboral de más de tres meses ◯ Paro con subsidio ◯ Paro sin subsidio ◯ Datos insuficientes

¿Se considera una persona tensa y/o agresiva? Puntuase de 0 (más relajado) a 10 (más competitivo)

Qué trabajo concreto hace o hacía

Qué trabajo concreto hace o hacía el/la cabeza de familia

¿Algún familiar directo (padres, hermanos, hijos, etc...) ha fallecido por causas cardíacas, o ha tenido algún problema cardíaco?

◯ sí, antes de los 55 años (varones) / 65 años (mujeres) ◯ sí, después de los 55 años (varones) / 65 años (mujeres)
◯ no ◯ Datos insuficientes

¿Ha sido usted informado por personal sanitario, que haya tenido alguna vez arritmias o alguna enfermedad cardíaca?

◯ sí ◯ no ◯ datos insuficientes

Diagnóstico

¿Algún familiar directo (padres, hermanos, hijos...) ha tenido algún accidente vascular cerebral?

◯ sí, antes de los 55 años ◯ no ◯ sí, después de los 55 años ◯ datos insuficientes

¿Algún familiar directo (padres, hermanos, hijos...) tiene el colesterol elevado?

◯ sí, antes de los 55 años ◯ sí, después de los 55 años ◯ no ◯ datos insuficientes

¿Algún familiar directo (padres, hermanos, hijos...) tiene la tensión arterial alta?

◯ sí, antes de los 55 años ◯ sí, después de los 55 años ◯ no ◯ datos insuficientes

¿Algún familiar directo (padres, hermanos, hijos...) tiene o ha tenido cáncer?

◯ sí, antes de los 55 años ◯ sí, después de los 55 años ◯ no ◯ datos insuficientes

¿Se cansa excesivamente o le falta el aire al realizar alaún eiercicio (subir escaleras, caminar, etc.)?

◯ No disnea
◯ Disnea a grandes esfuerzos (bailar, caminar durante media hora, trabajos de jardinería, etc.)
◯ Disnea a moderados esfuerzos (ducharse, vestirse,etc.)
◯ Disnea a mínimos esfuerzos (cualquier actividad, levantarse de la cama)
◯ Disnea sin especificar grado
◯ Datos insuficientes

¿Algún médico le ha diagnosticado de alguna de estas enfermedades? Puede haber más de una respuesta.

◯ Embolia pulmonar ◯ Trombosis venosa profunda ◯ Cataratas
◯ Aneurisma de aorta ◯ Bronquitis crónica - Enfisema ◯ Apneas del sueño
◯ Insuficiencia cardíaca izquierda ◯ Depresión ◯ Cáncer o Tumores

Edad del diagnóstico: ☐☐ años

Solo mujeres: **¿Que edad tenía cuando inició la menopausia?** ☐☐ años

¿Le ha molestado a ud. alguna vez la gente criticándole su forma de beber?

◯ sí ◯ no ◯ datos insuficientes

¿Ha tenido ud. la impresión de que debería beber menos?

◯ sí ◯ no ◯ datos insuficientes

¿Se ha sentido alguna vez mal o culpable por su costumbre de beber?

◯ sí ◯ no ◯ datos insuficientes

¿Alguna vez lo primero que ha hecho por la mañana ha sido beber para calmar los nervios o para librarse de una resaca?

◯ sí ◯ no ◯ datos insuficientes

Durante el último mes, ¿Ha tomado algún medicamento de los siguientes?

Aspirina, Adiro o similar	◯ sí	◯ no	◯ no sabe / no contesta
Otras medicinas para aliviar el dolor o la fiebre	◯ sí	◯ no	◯ no sabe / no contesta
Tranquilizantes, sedantes, pastillas para la ansiedad, pastillas para dormir.	◯ sí	◯ no	◯ no sabe / no contesta
Vitaminas o minerales	◯ sí	◯ no	◯ no sabe / no contesta
Medicamentos para el corazón	◯ sí	◯ no	◯ no sabe / no contesta
Medicamentos para la presión arterial	◯ sí	◯ no	◯ no sabe / no contesta
Medicamentos para el colesterol	◯ sí	◯ no	◯ no sabe / no contesta
Insulina	◯ sí	◯ no	◯ no sabe / no contesta
Medicamentos parala diabetes (diferentes de la insulina)	◯ sí	◯ no	◯ no sabe / no contesta
Solo mujeres: Tratamiento hormonal	◯ sí	◯ no	◯ no sabe / no contesta
Otros	◯ sí	◯ no	◯ no sabe / no contesta

En caso afirmativo, nombre del medicamento/s

indicar el nombre del fármaco, la dosis y el tiempo del tratamiento en años

LOS TRATAMIENTOS ANOTADOS POR EL PACIENTE DEBEN SER CONFIRMADOS POR LA ENFERMERA A PARTIR DE LA HISTORIA CLÍNICA DEL CENTRO DE SALUD

EXPLORACIÓN FÍSICA

Altura ___ cm **Cintura** ___ cm **Cadera** ___ cm

Peso ___ kg **Índice tobillo-brazo** ___ cm

		PAS	PAD	FC
Brazo no dominante	**1**			
(paciente sentado)	**2**			
Brazo izquierdo	**1**			
(paciente decubito supino	**2**			
Brazo derecho	**1**			
(paciente decubito supino)	**2**			
Tobillo izquierdo	**1**			
(paciente decubito supino)	**2**			
Tobillo derecho	**1**			
(paciente decubito supino)	**2**			

ITB Izquierdo (PAS mayor del tobillo izquierdo / PAS mayor de los brazos) ___,___

ITB Derecho (PAS mayor del tobillo derecho / PAS mayor de los brazos) ___,___

APPENDIX 2.

FOOD FREQUENCIE QUESTIONNAIRE

IDENTIFICACIÓN DEL PARTICIPANTE

NODO
01. Andalucía-Málaga
02. Andalucía-Sevilla-San Pablo
03. Andalucía-Sevilla-V. Rocío
04. Baleares
05. Catalunya-Barna Norte
06. Catalunya-Barna Sur
07. Catalunya-Reus-Tarragona
08. Madrid Norte
09. Madrid Sur
10. Navarra
11. País Vasco
12. Valencia

marque así

así no marque

NODO | CENTRO | MÉDICO | PACIENTE | VISITA

PÁGINA 1

Por favor, marque una única opción para cada alimento.

Para cada alimento, marque el recuadro que indica la frecuencia de consumo **por término medio** durante el **año pasado**. Se trata de tener en cuenta también la variación verano/invierno. Por ejemplo, si toma helados 4 veces/semana sólo durante los 3 meses de verano, el uso promedio al año es 1/semana

	CONSUMO MEDIO DURANTE EL AÑO PASADO								
	NUNCA O CASI NUNCA	AL MES	A LA SEMANA			AL DÍA			
		1 - 3	1	2 - 4	5 - 6	1	2 - 3	4 - 6	6+
I. LÁCTEOS									
1. Leche entera (1 taza, 200 cc)									
2. Leche semidesnatada (1 taza, 200 cc)									
3. Leche descremada (1 taza, 200 cc)									
4. Leche condensada (1 cucharada)									
5. Nata o crema de leche (1/2 taza)									
6. Batidos de leche (1 vaso, 200 cc)									
7. Yogurt entero (1, 125 gr.)									
8. Yogurt descremado (1, 125 gr.)									
9. Petit suisse (1, 55 gr.)									
10. Requesón o cuajada (1/2 taza)									
11. Queso en porciones o cremoso (1, porción 25 gr.)									
12. Otros quesos: curados, semicurados (Manchego, Bola, Emmental...) (50 gr.)									
13. Queso blanco o fresco (Burgos, cabra...) (50 gr.)									
14. Natillas, flan, puding (1, 130 cc)									
15. Helados (1 cucurucho)									

Un plato o ración de 100-150 gr, excepto cuando se indique otra cosa	NUNCA O CASI NUNCA	AL MES	A LA SEMANA			AL DÍA			
		1 - 3	1	2 - 4	5 - 6	1	2 - 3	4 - 6	6+
II. HUEVOS, CARNES, PESCADOS									
16. Huevos de gallina (uno)									
17. Pollo o pavo CON piel (1 ración o pieza)									
18. Pollo o pavo SIN piel (1 ración o pieza)									
19. Carne de ternera o vaca (1 ración)									
20. Carne de cerdo (1 ración)									
21. Carne de cordero (1 ración)									
22. Conejo o liebre (1 ración)									
23. Hígado (ternera, cerdo, pollo) (1 ración)									
24. Otras vísceras (sesos, corazón, mollejas) (1 ración)									
25. Jamón serrano o paletilla (1 loncha, 30 gr.)									
26. Jamón York, jamón cocido (1 loncha, 30 gr.)									
27. Carnes procesadas (salchichón, chorizo, morcilla, mortadela, salchichas, butifarra, sobrasada, 50 gr.)									
28. Patés, foie-gras (25 gr.)									
29. Hamburguesa (una, 50 gr.), albóndigas (3 unidades)									
30. Tocino, bacon, panceta (50 gr.)									
31. Pescado blanco: mero, lenguado, besugo, merluza, pescadilla,... (1 plato, pieza o ración)									
32. Pescado azul: sardinas, atún, bonito, caballa, salmón (1 plato, pieza o ración 130 gr.)									
33. Pescados salados: bacalao, salazones (1 ración, 60 gr. en seco)									
34. Ostras, almejas, mejillones y similares (6 unidades)									
35. Calamares, pulpo, chipirones, jibia (sepia) (1 ración, 200 gr.)									
36. Crustáceos: gambas, langostinos, cigalas, etc. (4-5 piezas, 200 gr.)									
37. Pescados y mariscos enlatados al natural (sardinas, anchoas, bonito, atún) (1 lata pequeña o media lata normal, 50 gr.)									
38. Pescados y mariscos en aceite (sardinas, anchoas, bonito, atún) (1 lata pequeña o media lata normal, 50 gr.)									

Por favor, marque una única opción para cada alimento.

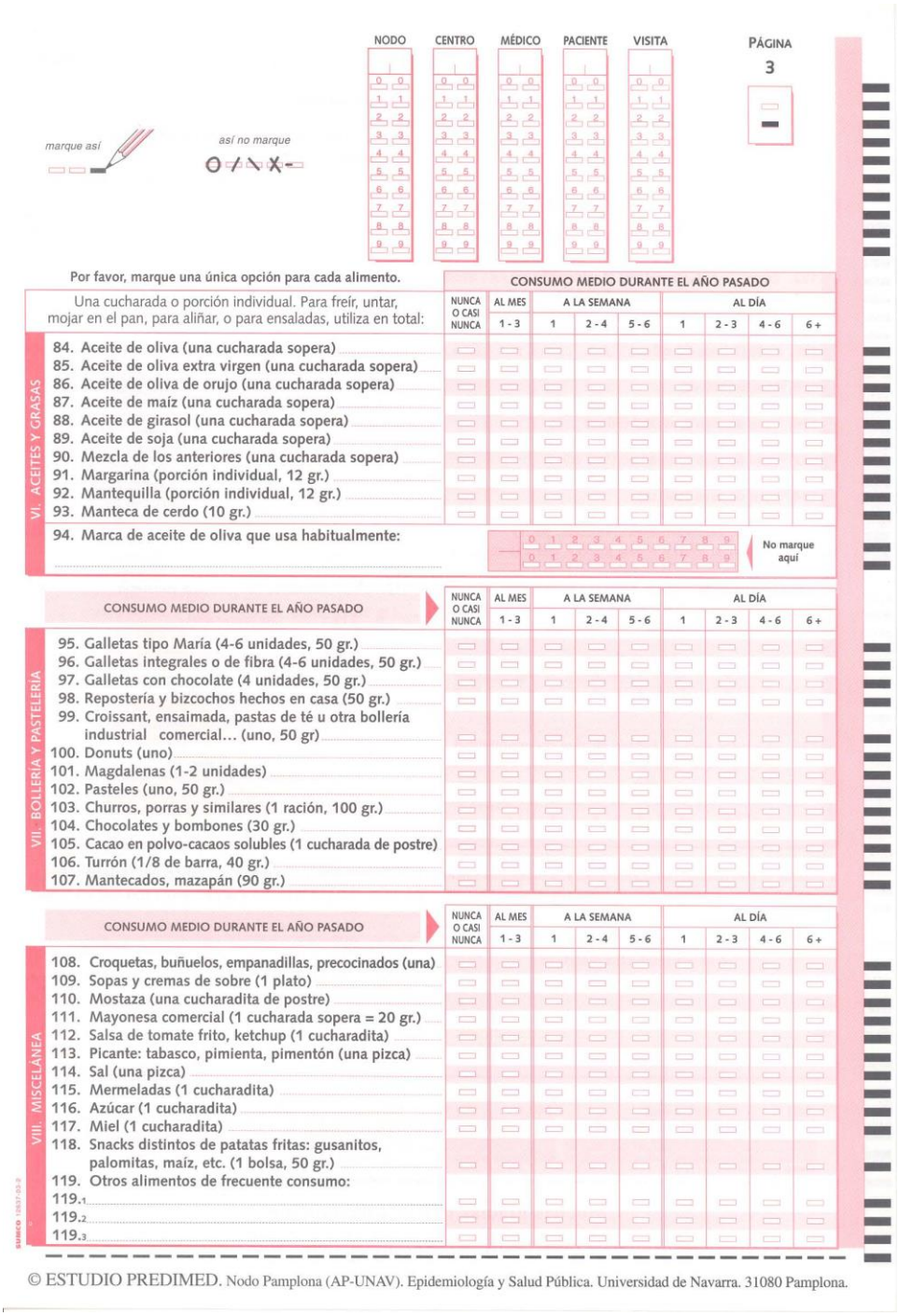
	Un plato o ración de 200 grs, excepto cuando se indique	CONSUMO MEDIO DURANTE EL AÑO PASADO								
		NUNCA O CASI NUNCA	AL MES	A LA SEMANA			AL DÍA			
			1 - 3	1	2 - 4	5 - 6	1	2 - 3	4 - 6	6 +
III. VERDURAS Y HORTALIZAS	39. Acelgas, espinacas									
	40. Col, coliflor, brócoles									
	41. Lechuga, endivias, escarola (100 gr.)									
	42. Tomate crudo (1, 150 gr)									
	43. Zanahoria, calabaza (100 gr.)									
	44. Judías verdes									
	45. Berenjenas, calabacines, pepinos									
	46. Pimientos (150 gr.)									
	47. Espárragos									
	48. Gazpacho andaluz (1 vaso, 200 gr.)									
	49. Otras verduras (alcachofa, puerro, cardo, apio)									
	50. Cebolla (media unidad, 50 gr.)									
	51. Ajo (1 diente)									
	52. Perejil, tomillo, laurel, orégano, etc. (una pizca)									
	53. Patatas fritas comerciales (1 bolsa, 50 gr.)									
	54. Patatas fritas caseras (1 ración, 150 gr.)									
	55. Patatas asadas o cocidas									
	56. Setas, níscalos, champiñones									

	Una pieza o ración	CONSUMO MEDIO DURANTE EL AÑO PASADO								
		NUNCA O CASI NUNCA	AL MES	A LA SEMANA			AL DÍA			
			1 - 3	1	2 - 4	5 - 6	1	2 - 3	4 - 6	6 +
IV. FRUTAS	57. Naranja (una), pomelo (una), o mandarinas (dos)									
	58. Plátano (uno)									
	59. Manzana o pera (una)									
	60. Fresas/fresones (6 unidades, 1 plato postre)									
	61. Cerezas, picotas, ciruelas (1 plato de postre)									
	62. Melocotón, albaricoque, nectarina (una)									
	63. Sandía (1 tajada, 200-250 gr.)									
	64. Melón (1 tajada, 200-250 gr.)									
	65. Kiwi (1 unidad, 100 gr.)									
	66. Uvas (un racimo, 1 plato postre)									
	67. Aceitunas (10 unidades)									
	68. Frutas en almíbar o en su jugo (2 unidades)									
	69. Dátiles, higos secos, uvas-pasas, ciruelas-pasas (150 gr.)									
	70. Almendras, cacahuetes, avellanas, pistachos, piñones (30 gr.)									
	71. Nueces (30 gr.)									

	72. ¿Cuántos días a la semana toma fruta como postre?		0	1	2	3	4	5	6	7

	Un plato o ración (150 gr.)	CONSUMO MEDIO DURANTE EL AÑO PASADO								
		NUNCA O CASI NUNCA	AL MES	A LA SEMANA			AL DÍA			
			1 - 3	1	2 - 4	5 - 6	1	2 - 3	4 - 6	6 +
V. LEGUMBRES Y CEREALES	73. Lentejas (1 plato, 150 gr. cocidas)									
	74. Alubias (pintas, blancas o negras) (1 plato, 150 gr. cocidas)									
	75. Garbanzos (1 plato, 150 gr. cocidos)									
	76. Guisantes, habas (1 plato, 150 gr. cocidas)									
	77. Pan blanco, pan de molde (3 rodajas, 75 gr.)									
	78. Pan negro o integral (3 rodajas, 75 gr.)									
	79. Cereales desayuno (30 gr.)									
	80. Cereales integrales: muesli, copos avena, all-bran (30 gr.)									
	81. Arroz blanco (60 gr. en crudo)									
	82. Pasta: fideos, macarrones, espaguetis, otras (60 gr. en crudo)									
	83. Pizza (1 ración, 200 gr.)									

SUMCO 12637-03 (Ref.) 1



NODO | CENTRO | MÉDICO | PACIENTE | VISITA | PÁGINA 3

marque así | así no marque

Por favor, marque una única opción para cada alimento.

Una cucharada o porción individual. Para freír, untar, mojar en el pan, para aliñar, o para ensaladas, utiliza en total:	CONSUMO MEDIO DURANTE EL AÑO PASADO: NUNCA O CASI NUNCA	AL MES 1 - 3	A LA SEMANA 1	A LA SEMANA 2 - 4	A LA SEMANA 5 - 6	AL DÍA 1	AL DÍA 2 - 3	AL DÍA 4 - 6	AL DÍA 6+
VII. ACEITES Y GRASAS									
84. Aceite de oliva (una cucharada sopera)									
85. Aceite de oliva extra virgen (una cucharada sopera)									
86. Aceite de oliva de orujo (una cucharada sopera)									
87. Aceite de maíz (una cucharada sopera)									
88. Aceite de girasol (una cucharada sopera)									
89. Aceite de soja (una cucharada sopera)									
90. Mezcla de los anteriores (una cucharada sopera)									
91. Margarina (porción individual, 12 gr.)									
92. Mantequilla (porción individual, 12 gr.)									
93. Manteca de cerdo (10 gr.)									
94. Marca de aceite de oliva que usa habitualmente:									

No marque aquí

CONSUMO MEDIO DURANTE EL AÑO PASADO	NUNCA O CASI NUNCA	AL MES 1 - 3	A LA SEMANA 1	A LA SEMANA 2 - 4	A LA SEMANA 5 - 6	AL DÍA 1	AL DÍA 2 - 3	AL DÍA 4 - 6	AL DÍA 6+
VII. BOLLERÍA Y PASTELERÍA									
95. Galletas tipo María (4-6 unidades, 50 gr.)									
96. Galletas integrales o de fibra (4-6 unidades, 50 gr.)									
97. Galletas con chocolate (4 unidades, 50 gr.)									
98. Repostería y bizcochos hechos en casa (50 gr.)									
99. Croissant, ensaimada, pastas de té u otra bollería industrial comercial... (uno, 50 gr)									
100. Donuts (uno)									
101. Magdalenas (1-2 unidades)									
102. Pasteles (uno, 50 gr.)									
103. Churros, porras y similares (1 ración, 100 gr.)									
104. Chocolates y bombones (30 gr.)									
105. Cacao en polvo-cacaos solubles (1 cucharada de postre)									
106. Turrón (1/8 de barra, 40 gr.)									
107. Mantecados, mazapán (90 gr.)									

CONSUMO MEDIO DURANTE EL AÑO PASADO	NUNCA O CASI NUNCA	AL MES 1 - 3	A LA SEMANA 1	A LA SEMANA 2 - 4	A LA SEMANA 5 - 6	AL DÍA 1	AL DÍA 2 - 3	AL DÍA 4 - 6	AL DÍA 6+
VIII. MISCELÁNEA									
108. Croquetas, buñuelos, empanadillas, precocinados (una)									
109. Sopas y cremas de sobre (1 plato)									
110. Mostaza (una cucharadita de postre)									
111. Mayonesa comercial (1 cucharada sopera = 20 gr.)									
112. Salsa de tomate frito, ketchup (1 cucharadita)									
113. Picante: tabasco, pimienta, pimentón (una pizca)									
114. Sal (una pizca)									
115. Mermeladas (1 cucharadita)									
116. Azúcar (1 cucharadita)									
117. Miel (1 cucharadita)									
118. Snacks distintos de patatas fritas: gusanitos, palomitas, maíz, etc. (1 bolsa, 50 gr.)									
119. Otros alimentos de frecuente consumo:									
119.1									
119.2									
119.3									

Por favor, marque una única opción para cada alimento.

IX. BEBIDAS

	CONSUMO MEDIO DURANTE EL AÑO PASADO								
	NUNCA O CASI NUNCA	AL MES	A LA SEMANA			AL DÍA			
		1 - 3	1	2 - 4	5 - 6	1	2 - 3	4 - 6	6+
120. Bebidas carbonatadas con azúcar: bebidas con cola, limonadas, tónicas, etc. (1 botellín, 200 cc)									
121. Bebidas carbonatadas bajas en calorías, bebidas light (1 botellín, 200 cc)									
122. Zumo de naranja natural (1 vaso, 200 cc)									
123. Zumos naturales de otras frutas (1 vaso, 200 cc)									
124. Zumos de frutas en botella o enlatados (200 cc)									
125. Café descafeinado (1 taza, 50 cc)									
126. Café (1 taza, 50 cc)									
127. Té (1 taza, 50 cc)									
128. Mosto (100 cc)									
129. Vaso de vino rosado (100 cc)									
130. Vaso de vino moscatel (50 cc)									
131. Vaso de vino tinto joven, del año (100 cc)									
132. Vaso de vino tinto añejo (100 cc)									
133. Vaso de vino blanco (100 cc)									
134. Vaso de cava (100 cc)									
135. Cerveza (1 jarra, 330 cc)									
136. Licores, anís o anisetes... (1 copa, 50 cc)									
137. Destilados: whisky, vodka, ginebra, coñac (1 copa, 50 cc)									

138. ¿A que edad empezó a beber alcohol (vino, cerveza o licores), incluyendo el que toma con las comidas con regularidad (más de siete "bebidas" a la semana)?

Edad (años)

Decena
Unidad

139. ¿Cuántos años ha bebido alcohol con regularidad (más de siete "bebidas" a la semana)?

Años

Decena
Unidad

119. Otros alimentos de frecuente consumo

119.1 (No marque aquí)

119.2 (No marque aquí)

119.3 (No marque aquí)

Si durante el año pasado tomó vitaminas y/o minerales (incluyendo calcio) o productos dietéticos especiales (salvado, aceite de onagra, leche con ácidos grasos omega-3, flavonoides, etc.), por favor indique la marca y la frecuencia con que los tomó:

Marcas de los suplementos de vitaminas o minerales o de los productos dietéticos	CONSUMO MEDIO DURANTE EL AÑO PASADO								
	NUNCA O CASI NUNCA	AL MES	A LA SEMANA			AL DÍA			
		1 - 3	1	2 - 4	5 - 6	1	2 - 3	4 - 6	6+
140.									
140.1									
140.2									

140 (No marque aquí)

140.1 (No marque aquí)

140.2 (No marque aquí)

SUMCO 12687-03-(Pet. 2)

Muchas gracias por su colaboración

APPENDIX 3.

14-ITEM MEDITERRANEAN DIET ADHERENCE QUESTIONNAIRE

ESTUDIO PREDIMED

Cumplimiento de la dieta

Identificador del participante:

Nodo _____ C.Salud _____ Médico _____ Paciente _____ Visita _____

Nodo: anotar el número de nodo correspondiente.
01. Andalucía - Málaga / 02. Andalucía - Sevilla - S.Pablo / 03. Andalucía - Sevilla - V.Rocío / 04. Baleares / 05. Cataluña - Barcelona norte / 06. Cataluña - Barcelona Sur / 07. Cataluña - Reus - Tarragona / 08. Madrid Norte / 09. Madrid Sur / 10. Navarra / 11. País Vasco / 12. Valencia

C.Salud: anotar el número del centro de salud correspondiente.

Médico: anotar el número del médico correspondiente.

Paciente: anotar el número del paciente correspondiente.

Visita: anotar el número de visita correspondiente.
00. Inclusión - exclusión / 01. Visita Inicial / 02. Visita 3 meses / 03. Visita 1 año / 04. Visita 2 años / 05. Visita 3años

Fecha del examen

____ / ____ /200__
Día Mes Año

1. ¿Usa usted el aceite de oliva como principal grasa para cocinar?	Sí = 1 punto	☐
2. ¿Cuanto aceite de oliva consume en total al día (incluyendo el usado para freir, comidas fuera de casa, ensaladas, etc.)?	4 o más cucharadas = 1 punto	☐
3. ¿Cuantas raciones de verdura u hortalizas consume al día? (las guarniciones o acompañamientos = 1/2 ración) 1 ración = 200g.	2 o más (al menos una de ellas en ensalada o crudas) = 1 punto	☐
4. ¿Cuantas piezas de fruta (incluyendo zumo natural) consume al día?	3 o más al dia = 1 punto	☐
5. ¿Cuantas raciones de carnes rojas, hamburguesas, salchichas o embutidos consume al día? (ración: 100 - 150 g)	menos de 1 al dia = 1 punto	☐
6. ¿Cuantas raciones de mantequilla, margarina o nata consume al día? (porción individual: 12 g)	menos de 1 al dia = 1 punto	☐
7. ¿Cuantas bebidas carbonatadas y/o azucaradas (refrescos, colas, tónicas, bitter) consume al día?	menos de 1 al dia = 1 punto	☐
8. ¿Bebe usted vino? ¿Cuánto consume a la semana?	7 o más vasos a la semana = 1 punto	☐
9. ¿Cuantas raciones de legumbres consume a la semana? (1 plato o ración de 150 g)	3 o más a la semana = 1 punto	☐
10. ¿Cuantas raciones de pescado-mariscos consume a la semana? (1 plato pieza o ración: 100 - 150 de pescado o 4-5 piezas o 200 g de marisco)	3 o más a la semana = 1 punto	☐
11. ¿Cuantas veces consume reposteria comercial (no casera) como galletas, flanes, dulce o pasteles a la semana?	menos de 2 a la semana = 1 punto	☐
12. ¿Cuantas veces consume frutos secos a la semana? (ración 30 g)	3 o más a la semana = 1 punto	☐
13. ¿Consume usted preferentemente carne de pollo, pavo o conejo en vez de ternera, cerdo, hamburguesas o salchichas? (carne de pollo: 1 pieza o ración de 100 - 150 g)	Sí = 1 punto	☐
14. ¿Cuantas veces a la semana consume los vegetales cocinados, la pasta, arroz u otros platos aderezados con salsa de tomate, ajo, cebolla o puerro elaborada a fuego lento con aceite de oliva (sofrito)?	2 o más a la semana = 1 punto	☐

APPENDIX 4.

PHYSICAL ACTIVITY QUESTIONNAIRE

ESTUDIO PREDIMED — **Cuestionario de actividad física**

Identificador del participante: Nodo | C.Salud | Médico | Paciente | Visita

Fecha del examen Dia / Mes / Año

DNI

CIP

CUESTIONARIO DE ACTIVIDAD FÍSICA EN EL TIEMPO LIBRE DE MINNESOTA

A continuación encontrara un cuadro con un listado de actividades fisicas y unas columnas con periodos de tiempo de realización de las mismas(semana,mes,trimestre y año). Cada columna esta dividida en dias y minutos.
La forma de rellenar el cuestionario es la siguiente:
1. Se lee atentamente cada actividad una a una y cuando se encuentre una que se haya realizado durante la última semana,con números claros y sin salirse del recuadro se rellenan las casillas correspondientes a los dias y minutos.
2. Seguidamente se repite la misma acción para el último mes,el último trimestre y el último año.
Ha de tener en cuenta que si ha realizado algúna actividad la última semana supone tambíen que la ha realizado el último mes,trimestre y año.
Para asegurar la uniformidad de la información recogida consideramos que:
- cada piso de escaleras = 1/2 min.
- una vuelta en esqui acuático = 5 mn.
- un set de tenis indivdual = 20 min.
- un set de tenis dobles = 15 min.
- golf 9 hoyos = 90 min.

Ejemplo:

Una persona que:

- durante la última semana ha ido a caminar media hora cada dia menos el fin de semana, ha de anotar un 5 en la columna de dias de práctica a la semana y 30 en minutos/dia de practica. Si durante el último año también ha ido a caminar pero durante 2 meses en el verano no ha hecho esta actividad , tendra que anotar 200 en la columna de dias de practica al año y 30 en minutos / dia de practica .
- durante la última semana ha subido 2 veces al dia 2 pisos por la escalera a de anotar un 7 en la columna de dias de práctica a la semana y 2 a minutos/ dia de práctica. Si esta actividad la repite todo el año,tendra que anotar 365 en la columna dias de práctica al año y 2 en minutos / dia de práctica.

ACTIVIDADES FÍSICAS	SEMANA		AÑO	
	DIAS DE PRACTICA	MINUTOS/DIA DE PRACTICA	DIAS DE PRACTICA	MINUTOS/DIA DE PRACTICA
ANDAR/BAILAR/SUBIR ESCALERAS				
1.Pasear	5	30	200	30
5.Subir escaleras	7	2	365	2

ACTIVIDADES FÍSICAS	SEMANA		AÑO	
	DIAS DE PRACTICA	MINUTOS/DIA DE PRACTICA	DIAS DE PRACTICA	MINUTOS/DIA DE PRACTICA
ANDAR/BAILAR/SUBIR ESCALERAS				
1.Pasear				
2.Andar de casa al trabajo y del trabajo a casa o en periodos de descanso del mismo				
3.Andar (llevando carrito de la compra)				
4.Andar (llevando bolsas de la compra)				
5.Subir escaleras				
6.Andar campo a través				
7.Excursiones con mochila				
8.Escalar montañas				
9.Ir en bicicleta al trabajo				
10.Bailar				
11.Aeróbic o ballet				
12.Jugar con los niños (corriendo, saltando,..)				
EJERCICIOS DE MANTENIMIENTO GENERAL				
13.Hacer ejercicio en casa				
14.Hacer ejercicio en un gimnasio				
15.Caminar deprisa				
16.Trotar ("Jogging")				
17.Correr 8-11 km/h				
18.Correr 12-16 km/h				
19.Levantar pesas				
ACTIVIDADES ACUÁTICAS				
20.Esquí acuático				
21.Surf				
22.Navegar a vela				
23.Ir en canoa o remar (por distracción)				
24.Ir en canoa o remar (en competición)				
25.Hacer un viaje en canoa				

ACTIVIDADES FÍSICAS	SEMANA		AÑO	
	DIAS DE PRACTICA	MINUTOS/DIA DE PRACTICA	DIAS DE PRACTICA	MINUTOS/DIA DE PRACTICA
26.Nadar (más de 150 metros en piscina)				
27.Nadar en el mar				
28.Bucear				
DEPORTES DE INVIERNO				
29.Esquiar				
30.Esquí de fondo				
31.Patinar (ruedas o hielo)				
OTRAS ACTIVIDADES				
32.Montar a caballo				
33.Jugar a los bolos				
34.Balonvolea				
35.Tenis de mesa				
36.Tenis individual				
37.Tenis dobles				
38.Badminton				
39.Baloncesto (sin jugar partido)				
40.Baloncesto (jugando un partido)				
41.Baloncesto (actuando de árbitro)				
42.Squash				
43.Fútbol				
44.Golf (llevando el carrito)				
45.Golf (andando y llevando los palos)				
46.Balonmano				
47.Petanca				
48.Artes marciales				
49.Motociclismo				
50.Ciclismo de carretera o montaña				

ACTIVIDADES FÍSICAS	SEMANA		AÑO	
	DIAS DE PRACTICA	MINUTOS/DIA DE PRACTICA	DIAS DE PRACTICA	MINUTOS/DIA DE PRACTICA
ACTIVIDADES EN EL JARDÍN				
51.Cortar el césped con máquina				
52.Cortar el césped manualmente				
53.Limpiar y arreglar el jardín				
54.Cavar el huerto				
55.Quitar nieve con pala				
TRABAJOS Y ACTIVIDADES CASERAS				
56.Trabajos de carpintería dentro de casa				
57.Trabajos de carpintería (exterior)				
58.Pintar dentro de casa				
59.Pintar fuera de casa				
60.Limpiar la casa				
61.Mover muebles				
CAZA Y PESCA				
62.Tiro con pistola				
63.Tiro con arco				
64.Pescar en la orilla del mar				
65.Pescar con botas altas dentro del río				
66.Caza menor				
67.Caza mayor (ciervos, osos...)				
OTROS (ESPECIFICAR)				

APPENDIX 5.

RELATED SCIENTIFIC CONTRIBUTION

Journal Articles

Authors: Juanola-Falgarona M, Salas-Salvadó J, Estruch R, Portillo MP, Casas R, Miranda J, Martínez-González MA, Bulló M.
Title: Association between dietary phylloquinone intake and peripheral metabolic risk markers related to insulin resistance and diabetes in elderly subjects at high cardiovascular risk.
Journal: Cardiovasc Diabetol. Año: 2013 Jan 8;12:7. **Impact Factor**: 4.21

Authors: Guasch-Ferré M, Bulló M, Martínez-González MÁ, Ros E, Corella D, Estruch R, Fitó M, Arós F, Wärnberg J, Fiol M, Lapetra J, Vinyoles E, Lamuela-Raventós RM, Serra-Majem L, Pintó X, Ruiz-Gutiérrez V, Basora J, Salas-Salvadó J; PREDIMED study group.
Title: Frequency of nut consumption and mortality risk in the PREDIMED nutrition intervention trial.
Journal: BMC Med. Año: 2013 Jul 16;11:164. **Impact Factor**: 6.68

Authors: Díaz-López A, Bulló M, Juanola-Falgarona M, Martínez-González MA, Estruch R, Covas MI, Arós F, Salas-Salvadó J.
Title: Reduced serum concentrations of carboxylated and undercarboxylated osteocalcin are associated with risk of developing type 2 diabetes mellitus in a high cardiovascular risk population: a nested case-control study.
Journal: J Clin Endocrinol Metab. Año: 2013 Nov;98(11):4524-31 **Impact Factor**: 6.43

Authors: Juanola-Falgarona M, Cándido-Fernández J, Salas-Salvadó J, Martínez-González MA, Estruch R, Fiol M, Arija-Val V; Mònica Bulló; PREDIMED Study Investigators.
Title: Association between serum ferritin and osteocalcin as a potential mechanism explaining the iron-induced insulin resistance.
Journal: PLoS One. Año: 2013 Oct 22;8(10):e76433. **Impact Factor**: 3.73

Authors: Juanola-Falgarona M, Salas-Salvadó J, Martínez-González MÁ, Corella D, Estruch R, Ros E, Fitó M, Arós F, Gómez-Gracia E, Fiol M, Lapetra J, Basora J, Lamuela-Raventós RM, Serra-Majem L, Pintó X, Muñoz MÁ, Ruiz-Gutiérrez V, Fernández-Ballart J, Bulló M.
Title: Dietary intake of vitamin K is inversely associated with mortality risk.
Journal: J Nutr. Año: 2014 May;144(5):743-50. **Impact Factor**: 4.2

Authors: Hernández-Alonso P, Salas-Salvadó J, Baldrich-Mora M, Juanola-Falgarona M, Bulló M.
Title: Beneficial Effect of Pistachio Consumption on Glucose Metabolism, Insulin Resistance, Inflammation, and Related Metabolic Risk Markers: a Randomized Clinical Trial.
Journal: Diabetes Care.2014 Aug pii: DC_141431. [Epub ahead of print]. **Impact Factor:** 8.1

Authors: Bulló M, Juanola-Falgarona M, Hernández-Alonso P, Salas-Salvadó J. **Title:** Nutritional attributes and health effects of pistachio nuts. **Journal:** Br J Nutr. 2014 [Accepted] **Impact Factor:** 3.342

Book Chapters

Authors: Juanola-Falgarona M, Bulló M
Chapter Title: Cuantificación de grasa en heces [Quantification of fecal feces].
Book Title: Nutrición y dietética clínica [Nutrition and clinical dietetics]. 3rd Edition. Spain.

Poster Presentations

18th European Congress on Obesity
25-28 of May 2011; Istambul (Turkey)

Authors: Bulló M, Juanola-Falgarona M, Basora J, Covas M, Salas-Salvadó J.
Title: Bone quantitative ultrasound measurements in relation to the metabolic syndrome and type 2 diabetes mellitus in a cohort of elderly subjects at high risk of cardiovascular disease from the PREDIMED study.

X Congreso SEEDO (Sociedad Española para el Estudio De la Obesidad)
19 – 21 of October 2011; Barcelona (Spain)
Authors: Bulló M, Casas R, del Puy Portillo M, Basora J, Estruch R, García-Arellano A, Lasa A, Juanola-Falgarona M, Arós F, Salas-Salvadó J.
Title: Relación entre el índice glucémico o la carga glucémica de la dieta, las concentraciones de adipoquinas y otros marcadores metabólicos en sujetos adultos.

X Congreso SEEDO (Sociedad Española para el Estudio De la Obesidad)
19 – 21 of October 2011; Barcelona (Spain)
Authors: Juanola-Falgarona M, Ibarrola-Jurado N, Rabassa A, Díaz-López A, Aguilera N, Bulló M, Salas-Salvadó J
Title: Efecto del índice glucémico y la carga glucémica de la dieta sobre el peso corporal y los marcadores de inflamación: diseño de estudio.

11th European Nutrition Conference
26-29 of October 2011; Madrid (Spain)
Authors: Bulló M, Casas R, del Puy Portillo M, Basora J, Estruch R, García-Arellano A, Lasa A, Juanola-Falgarona M, Arós F, Salas-Salvadó J.
Title: Dietary glycemic index/load, peripheral adipokines and inflammatory markers in elderly subjects.

19th European Congress on Obesity
26-29 of May 2012; Lyon (France)

Authors: Juanola-Falgarona M, Salas-Salvadó J, Estruch R, Portillo MP, Casas R, Lasa A, Martínez-González MA, Bulló M.
Title: Association between dietary phylloquinone intake and peripheral metabolic risk markers related to insulin resistance and diabetes in elderly subjects at high cardiovascular risk.

XXV Congreso Nacional de la Sociedad Española de Arteriosclerosis
26-29 of June 2012; Reus (Spain)
Authors: Juanola-Falgarona M, Salas-Salvadó J, Estruch R, Portillo MP, Casas R, Lasa A, Martínez-González MA, Bulló M.
Title: Association between dietary phylloquinone intake and peripheral metabolic risk markers related to insulin resistance and diabetes in elderly subjects at high cardiovascular risk.

20th European Congress on Obesity
12-15 May 2013; Liverpool (UK)
Authors: Juanola-Falgarona M, Ibarrola-Jurado N, Salas-Salvadó J, Rabassa-Soler A, Bulló M.
Title: Effect of dietary glycemic index and glycemic load on body weight and cardiovascular risk factors: The GLYNDIET Study.

1er Congreso Medico-Quirugico de la Obesidad.
14-15th March, 2013, Madrid (Spain)
Authors: Juanola-Falgarona M, Fernández-Cándido J, Salas-Salvadó J, Martínez-González MA, Estruch R, Fiol M, Arija-Val V, Bulló M, For the PREDIMED Study Investigators.
Title: Association between serum ferritin and osteocalcin as a potential mechanism of iron-induced insulin resistance.

1st World Forum for Nutrition Research
20-21th May 2013, Reus (Spain)
Authors: Juanola-Falgarona M, Salas-Salvadó J, Estruch R, Portillo MP, Casas R, Lasa A, Martínez-González MA, Bulló M.

Title: Association between dietary phylloquinone intake and peripheral metabolic risk markers related to insulin resistance and diabetes in elderly subjects at high cardiovascular risk.

1st World Forum for Nutrition Research
20-21th May 2013
Authors: Juanola-Falgarona M, Salas-Salvadó J, Martínez-González Ma, Corella D, Ros E, Estruch R, Fitó M, Arós F, Wärnberg J, Bulló M.
Title: Dietary intake of phylloquinone in relation to all-cause mortality in a Mediterranean population at high cardiovascular risk.

20th International Congress of Nutrition
15-20 semptember, 2013, Granada (Spain)
Authors: Juanola-Falgarona M, Salas-Salvadó J, Martínez-González MA, Corella D, Ros E, Estruch R, Fitó M, Arós F, Wärnberg J, Fiol M, Lapetra J, Vinyoles E, Lamuela-Raventós RM, Serra-Majem L, Pintó X, Ruiz-Gutiérrez V, Basora J, Bulló M.
Title: Dietary intake of phylloquinone is related to a reduced risk of all-cause mortality: the predimed study.

20th International Congress of Nutrition
15-20 September, 2013, Granada (Spain)
Authors: Juanola-Falgarona M, Salas-Salvadó J, Estruch R, Portillo MP, Casas R, Lasa A, Martínez-González MA, Bulló M.
Title: Dietary intake of phylloquinone is associated to lower concentrations of metabolic markers in elderly subjects at high cardiovascular risk.

20th International Congress of Nutrition
15-20 September, 2013, Granada (Spain)
Authors: Juanola-Falgarona M, Fernández-Cándido J, Salas-Salvadó J, Martínez-González MA, Estruch R, Fiol M, Arija-Val V, Bulló M, For the PREDIMED Study Investigators

Title: Association between serum ferritin and osteocalcin as a potential mechanism of iron-induced insulin resistance.

III World Congress of Public Health Nutrition
9-12 November, 2014, Las Palmas de Gran Canaria (Spain)
Authors: Juanola-Falgarona M; Salas-Salvadó J; Buil-Cosiales P;Corella D; Estruch R; Emili Ros; Montserrat Fitó; Fernando Arós; Enrique Gómez-Gracia; Miquel Fiol; José Lapetra; Mònica Bulló on behalf of the PREDIMED Study Investigators.
Title: Dietary glycemic index and glycemic load are positively associated with risk of developing metabolic syndrome.